

How Much is Enough?

THE most respectable of all numbers games is the prediction of population, as in the United Kingdom. Unlike other forms of gaming, bingo or blackjack, for example, trying to tell how many young people will need desks in schools ten years ahead, or how many older people will need hospital beds in which to be sick, tends to be invested with all the propriety of social purpose. A demographer is a social scientist, not a gambler—that, at least, is what his friends and employers say. The latest attempt to estimate the future population of the United Kingdom, *Population Projections 1970–2010* prepared by the Government Actuary (HMSO, £1.20), goes a long way to suggest that the truth may be on the other side of the coin, and that the time has come for those who would predict the future population of a nation to throw a handful of dead leaves in the air and then count the number falling right side up.

The Government Actuary (a statistical analogue of an astronomer-royal not to be confused with the head of the British Government's Statistical Service) has on this occasion set out to estimate the population of the United Kingdom and the several parts of it (Ulster included) in the next forty years. Up to a point, the exercise makes sense, for more than half of the people who will still be alive in Britain in AD 2000 are alive already. Many of them are even middle-aged. To that extent, it is easy enough to estimate the population of old people's homes at the turn of the century. Unhappily, it is much more difficult to estimate how many young people there will be. Especially now that it has become unfashionable for the parents of large families to declare in public how great a claim they have made on future resources, and with women's liberation just around the corner, not even a Government Actuary can be sure what he intends by a population prediction for the year 2000.

The latest prediction is not merely uncertain but also as unoriginal as anybody could wish. For the United Kingdom as a whole, the population is expected to increase steadily from 55.8 million in 1970 (halfway through the year) to 58.9 million in 1981, 62.3 million in 1991 and 66.5 million in 2001. In other words, the increase of population is estimated to be about 20 per cent in the course of the next thirty years. In the circumstances, it is only proper to ask how accurate these estimates may be.

In the thirty years between now and the end of the century, rather more than 20 million people will die. Emigration will account for about 2 million more even if the growing political integration in Western Europe does not further stimulate the tendency for people born in Britain to earn their living abroad. During the same period and on the assumptions which the Government Actuary has made about the future fertility of the United Kingdom, something like 25 million people will be born or will immigrate into the United Kingdom. Quite apart from the uncertainties which there must be about the future trend of fertility, the balance of emigration and immigration may be a source of great error—the 1971 census shows an error of 500,000 on this score in the past

decade. In ordinary life, in a physics laboratory for example, nobody would complain if the Government Actuary had thrown up his hands in the face of these uncertainties and had declared that forecasting of the population of the United Kingdom thirty years from now would be impossible. The demographers, unfortunately, expect no less of themselves and their colleagues. The trouble, of course, is that the errors in such a process are so great that the forecast is in part at least a kind of guess.

Quite understandably, the Government Actuary bemoans the way in which the fertility of the women of the United Kingdom has fluctuated in the past few years. In the space of a quarter of a century, the number of births each year has fluctuated between less than 800,000 and rather more than 1 million.

In the mid-1960s, the official demographers were so impressed by the rapid growth of fertility that they were seduced into estimates of the population of the United Kingdom amounting to close on 80 million by 2000—estimates so alarming that they have since become a part of the popular mythology of population growth. In the event, not merely fertility but the number of births each year in the United Kingdom has since fallen steadily, yet even now the latest estimate of population is based on the assumption that this tendency will be reversed forthwith. In these circumstances, very few of those who put money on racehorses would be persuaded that it can be sensible to back the most bullish of the estimates which the Government Actuary has put forward. It is at least as good a bet that the population of the United Kingdom will be the same at the end of the century as it is at present. If there is a change, it will most probably consist of an increase of the proportions of old people and a corresponding decrease of young people.

The moral, which should be heeded not merely by the Government Actuary but by the three registrar-generals of the United Kingdom, not to mention such organizations as the Census Bureau in the United States and the Population Commission of the United Nations, is that there are serious limits on attempts to forecast the population of countries, regions or the world as a whole. It may be possible in advanced societies, where the death rate is reasonably predictable, to estimate the numbers of schoolchildren three or four years ahead or the numbers of old-age pensioners fifty years ahead, but the estimation of how many young people there will be by the end of the century requires a much better understanding of the motives which persuade couples in advanced societies to have children or to forswear them as well as a certain amount of luck. As it happens, this is the most notoriously unreliable parameter in the demography of the future. In the circumstances, might it not be a great saving of public funds if the Government Actuary and the other organizations which are tempted to follow in these inelegant footsteps—on this occasion, the Actuary has not even put forward an estimate of the extent to which he thinks his estimate may be uncertain—were to settle for more modest but more realistic goals in forecasting the population?



Science was a Sacred Cow

SIR FREDERICK DANTON, playing Caesar's wife as always, gave no tangible sign in his Fawley lecture last week of what his report on the administration of civil science will have to recommend when it is published (as the Government now promises) before the end of the year (see page 118). That is perhaps as well, for there is every prospect that the forbidden fruit, when eventually it is tasted, will be a disappointment—not so much a programme for change as a recipe for preserving the present state of affairs.

The strongest part of Sir Frederick's declaration was that in which he pleaded for a better appreciation of the place of science in the enterprise of modern civilization. In the long run, it may be more important that people should understand what value there is in science than that there should be a radical programme for the reconstruction of organizations such as the Science Research Council, the Council for Scientific Policy and even the University Grants Committee. What is the value of it all? And how does it come about that throughout the industrialized world, scientific enterprise is in the doldrums?

Much of what has happened is intrinsically a part of the scientific enterprise itself. Sir Frederick was right to say as much. The temper of science has changed enormously in half a century. The change consists simply in the organization of working scientists into teams and their congregation around important and expensive items of equipment. But it also follows that those who pay for the expensive apparatus, usually taxpayers, should increasingly ask difficult and obscure questions about the extent to which the community which pays the piper is able or even competent to call the tune. The endless preoccupation with the machinery for the administration of civil science, red herring though it may be, is one symptom of the public determination to extract what benefits there may be in an item of public expenditure which falls not far short of three per cent of the gross national product in countries such as Britain and the United States. It would of course be better for the community as well as for professional science if these questions could be directed more accurately to the problem of making the best use of civil science.

Sir Frederick Danton has a large part of the answer, for in his address last week he quite properly took the universities to task for failing to take a proper view of their chief function, the training of young people in science and related crafts. Two manifestations of this failure have been especially prominent in the past few years. First, university teachers and their students have fallen into the habit of bemoaning the difficulty of finding jobs in professional science, which amounts simply to a complaint about the difficulty of finding jobs for science graduates in research, development or higher education. Second, there is a growing torrent of complaint from employers and potential employers that the instruction offered to undergraduates in science is not such as to equip them for a wider life. Universities are still trying to provide students of science with training of the kind best suited for the winning of a Nobel prize. Yet what the students need is a blend of competence and knowledge

that will allow them to function well not merely as academics but in more practical jobs as well.

How is this to be achieved? Attempts at more flexible curricula have merely scratched the surface. What has become of the brave declarations by the Science Research Council that it would encourage radical innovations of the curriculum? A number of universities have broken a little new ground, but there is not much of it. Yet is it not in the immediate interests of the scientific enterprise that the quality of higher education in science should be rapidly changed? And how can this be done if the research councils still spend all their money on research as such and not on pedagogy in the widest sense?

Externally, there are still more serious problems to contend with. For lack of argument to the contrary, the impression has grown up that science is not so much a good thing as a bad thing. It tends to be forgotten that the "science" which has provoked the world population growth consists of the avoidance of avoidable disease, that the prosperity held responsible for air pollution and other evils has powerfully narrowed the gap between the rich and poor in advanced societies and that those societies now have a far greater capacity to help developing nations. To be sure, it remains to be seen whether in the few decades the full promise of what now appears possible will be realized, but there is at least a case for asking that professional scientists should play some part in advocating such a course. Sir Frederick Danton was right, last week, to remind them of where their duty lies.

100 Years Ago



It remains to be seen whether the Council will consent, at the bidding of the Senate, to rescind the regulations which they themselves freely passed in 1869, with the sanction of the Senate, viz. :—

"Women shall be admitted to the study of medicine in the University. The instruction of women for the profession of medicine shall be conducted in separate classes, confined entirely to women. The professors of the Faculty of Medicine shall, for this purpose, be permitted to have separate classes for women. All women attending such classes shall be subject to all the regulations now or at any future time in force in the University as to the matriculation of students, their attendance on classes, examination, or otherwise."

Any proposal for mixed classes of both sexes in purely medical subjects excites so great a repugnance both among the teachers and students of medicine that it would be extremely unwise to press it; but it will be observed that no such question has been raised here, and no such request has ever been made by the lady medical students
From Nature 4, 58, November 23, 1871.

OLD WORLD

SELECT COMMITTEE

Cash for Computers

THE establishment of a computer purchasing board is recommended to resolve the involved and intricate process by which the British government buys computers. In a report published yesterday the Select Committee on Science and Technology calls for an end to the present system that involves collaboration with several departments before an order is finally placed by the Stationery Office and it recommends that the purchasing board be directly responsible to parliament through the Civil Service Department (*The Prospects for the United Kingdom Computer Industry in the 1970s*, HMSO, £0.47).

A further recommendation is that the government maintains its present policy of giving preference to the British computer industry as it has done to ICL but that the system should be based differently to that operated at present. In particular, more government aid should be given in the form of grants and development contracts—and less at the tendering stage. This latter system has aroused a great deal of furore in past years, with IBM and Honeywell complaining that even though they contribute to the balance of payments in Britain they are unfairly discriminated against, claiming that they have to tender 25 per cent lower than their British competitors to land a contract (see *Nature*, **230**, 4; 1971).

To implement a policy of government support for the computer industry the committee recommends the establishment of a computer research and development board through which all government support for the computer industry will be channelled. The board will have to decide on the amount of support to be given to companies and in a proposed set of criteria companies whose parent bodies are outside Britain can qualify for support. In awarding contracts, however, the committee recommends that price and performance should be the prime consideration and that in some instances these should have overriding priority. These suggestions should go a long way towards mollifying companies such as IBM and Honeywell and should ensure that ICL will continue to be a viable entity.

The committee comes out strongly for an independent British computer industry and it says that the industry should not become dominated by foreign technology. To ensure this the committee says that a considerable research and development effort is required to the tune of at least £50 million a year supplied by the government. It considered that apart from the £13.5 million

that the government had already injected into ICL the support of the industry has been "derisory". The committee also pointed out that the original purpose of this grant was to improve the research and development facilities of the company but in fact it had gone to improve the financial resources of ICL after the merger of ICT, English Electric Computers and the computing interests of Plessey. There is at present no assurances that further aid will be given to the industry—which has amounted to only £3.2 million in six years—and the committee is concerned that even the present level of support could be cut.

The report comes out strongly in favour of government departments making use of independent software houses. The committee argues that the use of independent companies to supply computer programs and services will make for efficient use of government computers as well as strengthening the computer industry in Britain.

GRADUATE EMPLOYMENT

Significant Statistics

MORE first degree graduates of British universities took up further academic study or research in the pure sciences in 1969–70 than in 1968–69 but the number of men embarking on applied science research was smaller than in the previous year (*First Employment of University Graduates, 1969–70*, University Grants Committee, HMSO, £0.68).

The increase in the proportion of pure science graduates entering research during 1969–70—from 28.7 to 29.4 per cent for men and from 14.8 to 15.3 per cent for women—contrasts with a reduction in the percentage of all graduates entering research or further study which has been evident since 1964–65. Then, of the 27,549 first graduates of British universities, 5,682 students continued with further study whereas in 1969–70, 7,149 out of 47,584 graduates remained at university. Since 1966–67 the number of students entering research or academic study has remained substantially constant at a time when the total number of graduates has increased by more than 11,000.

The percentage of male applied scientists starting on research work decreased from 14.4 per cent in 1969 to 12.7 per cent in 1970, whereas the proportion of women graduates in applied science who started research increased slightly in the same period. The number of applied science graduates increased to 19.0 per cent in contrast to the number of graduates in pure science, which continued to drop—in 1969–70, 29.1 per cent of all degrees were granted in pure science compared with 30.1 per cent in 1968–69.

More than eleven thousand students

graduated with higher degrees in 1969–70 of which 64.6 per cent were in the sciences. Of the British students who obtained higher science degrees more than 22 per cent went into industry and 13.3 per cent went overseas. By contrast, only 7.9 per cent of arts higher degree graduates sought their first employment abroad.

INDUSTRIAL RELATIONS

Professionals' Plans

PLANS are firmly afoot to found a Confederation of Professional and Executive Associations. The confederation is essentially the brainchild of UKAPE, the United Kingdom Association of Professional Engineers, whose general secretary, Mr Kenneth Peplow, said last week that he hoped to see CPEA fully active by January 1, 1972. The aim of the confederation will be to provide the machinery for professional bodies to express their viewpoint on matters which affect them. Mr Peplow says that he has received about 90 enquiries from various bodies—not all of them professional associations—but that the founding members of CPEA will be UKAPE, the Association of Supervisory and Executive Engineers and the scarcely formed Association of Professional Scientists and Technologists (see *Nature*, **233**, 440; 1971).

Mr D. B. Sweaney, general secretary of the ASEE, said this week that the confederation would be a non-militant and non-political body with which employers could deal in wage negotiations and other matters as the member associations would give the confederation full negotiating rights on their behalf. One qualification for the confederation is that the associations must have a professional code of conduct and ethics, and it is this the sponsors feel that demarks associations from other trade unions. UKAPE and ASEE are fully in favour of the scheme, although Mr Barry Henman at APST was more cautious. APST has only been a corporate body for a few weeks and its initial recruiting drive is being launched this month, so that while APST "values a common front [with other professional associations] the decision to join must be decided by the governing body of APST and this has not yet been done". APST holds basically similar aims to UKAPE and its organization has no doubt been accelerated by the realization among scientists that once the new Industrial Relations Act comes into force scientists in industry will definitely be on the employees' side of the fence when it comes to wage bargaining.

The plans for the confederation are ambitious—Mr Peplow hopes it will come to include all professional associations—but the strength of the three

involved so far is not great—UKAPE has 11,000 members and ASEE about the same. Reaction from some quarters is far from enthusiastic — a spokesman for the TUC said “there is no need for it, we cater for professional bodies here”, and the reaction of Mr C. Cooper, deputy general secretary of the Institution of Professional Civil Servants, was that the scheme was “grandiose” and unnecessary as individual associations are quite capable of negotiating with employers and he doubted if there would be much recognition for the confederation.

METALS

Continuing Uncertainty

INTERNATIONAL NICKEL, the largest producer of nickel in the world, is being forced to cut down production because of a sharp decline in sales during 1971 and it seems that a cycle which started in 1966 when demand for nickel first began to outstrip supply has come full circle. International Nickel is now planning to reduce its output by 15 per cent by early 1972.

The nickel shortage of a few years ago was exacerbated by strikes at most of the principal mines in Ontario, Canada, which lasted for several months at the end of 1969. International Nickel was not the only company involved and Falconbridge—the third largest nickel producer in the world—was also badly affected. At that time, the output of International Nickel dropped to about 30 per cent of its previous level (£500 million a year) and production by Falconbridge was almost completely halted. Towards the end of 1969, the price in the free market (in which only about 10 per cent of the world's nickel is sold) rose to a level about seven times higher than the so-called producer price (£1,220 a metric ton) at which large companies like International Nickel sell their products. Users of nickel at that time could buy rationed quantities of nickel from large companies at the producer price or greater amounts in the free market at inflated prices.

Now the producer price is £1,246.50 a metric ton and the free market price is slightly lower than this. But the demand for nickel—more than 40 per cent of it is used in the production of stainless steel—has fallen off because of

the poor economic climate. Nickel consumers now see that world nickel supplies are plentiful and are happy to allow their own stocks to fall to quite low levels.

There are at last some signs that the sales of aluminium in Britain are picking up after a disastrous nine months for the industry that has seen the rate of growth of sales drop to around 1 per cent. This has led to stockpiling by the manufacturers and a slowing down in the time scale of bringing new smelters into operation. A spokesman for the British Aluminium Company said last week that it would be eighteen months before the situation was rectified, although it would be longer before the world-wide rate of expansion would be restored to its pre-1970 rate of 8 per cent.

In spite of these difficulties the posted price of aluminium remains at the 1970 price of £257 a metric ton although this hides the real situation where aluminium dealings are currently being conducted at up to £70 below this price. The stability in the price is one of the aluminium companies' selling points and the inroads made into the sales of copper in Britain during the past five years can be seen in the table.

Until recently Britain imported most of the 400,000 tons sold annually because of the large amount of electricity needed—16,000 to 18,000 kilowatt hours—to produce a ton of metal from alumina. Four years ago the government in an attempt to reduce Britain's balance of payments offered inducements to aluminium companies to build smelters in Britain. These plants are now becoming operational and when fully operational they should produce 300,000 tons a year that will reduce Britain's dollar drain by up to £40 million. The companies themselves will also save on import tariffs when Britain enters the European Economic Community.

The copper market is in its steadiest state for years. After the gradual decline of the past year the price seems to have settled at about £420 on the London Metal Exchange and no significant changes are expected in the near future.

The copper market is well known to be an early indicator of economic trends, and the low level of the market, compared with last year when the price at

one stage reached £749 a metric ton, is partially accounted for by the depressed state of the world economy. For the first time in some years there is an excess of supply over demand, partly due to new copper mines coming into production which were planned when copper prices were high and supplies were low in 1968 and 1969. The London Metal Exchange, which controls the price of 60 per cent of the world's copper, has reserve stocks at the moment of more than 132,000 tons, the highest ever, and until these begin to fall the price is unlikely to rise a great deal. It is thought in many quarters that a price of about £500 a metric ton can be expected by the middle of next year as it is assumed that the American economy will be re-inflated when the presidential election campaign begins.

Copper is the most volatile metal market for a number of reasons. The countries which supply the bulk of the world's copper—Zambia, Chile, Peru and the Congo—are not renowned for their political stability, and the copper industry seems to attract more than its fair share of strikes. Again, copper is not protected from speculators in the way that other metals are. Aluminium and nickel, for instance, are largely sold at the price the major producers agree between themselves and although price changes are usually large, it nevertheless remains constant for longish periods.

SCIENCE POLICY

Dainton on Science

SIR FREDERICK DANTON, chairman of the Council for Scientific Policy, believes that the current disenchantment with science arises because science was over-sold in the postwar years and because there is at present a “long term distaste if not active revulsion from science”. These views were expressed by Sir Frederick last week at the University of Southampton when he gave the annual Fawley lecture on “Science: Salvation or Damnation”.

Sir Frederick is nevertheless optimistic about the future even though he openly admitted that his lecture did “little more than list many maladies from which we suffer”. He believes that “knowledge is the best weapon to combat fear and therefore that if science is taught and practised imaginatively and with a sense of social responsibility, the present disenchantment with it will not long persist”.

The body of Sir Frederick's address reviewed the nature and development of science from the carefree days when a chemistry professor could ask his assistant to bring in his laboratory on a tray to the present, where in Britain £1,000 million a year is spent on research and development. Sir Frederick is being

Table 1 Metal Data 1966-71

Metal	Annual consumption UK		Price per tonne		
	1966 '000 metric tons	1970	1966	1970 £ sterling	1971
Aluminium	366.0	404.2	193	257	257
Nickel	34.4	34.7	691	1,268	1,268
Copper	592.5	546.5			418*

* Average figures.

† Average price for October.

realistic, however, when he states that historians will probably regard the 1970s as the time "when near adulation of science gave place to feelings ranging from grave doubts to at worst a neo-Luddism based on fear".

Sir Frederick is emphatic that the clock cannot be put back to remove the current disillusionment with science, and he stressed that "to attempt to stop any further scientific research is both wrong and impracticable". Sir Frederick also felt that it is impracticable to stop work on branches of science that "serve the baser needs of man and nation" because one cannot predict in advance the outcome of research. On accepting that scientific work must continue Sir Frederick asked whether the scientist has a moral right to suppress his findings and to stop pursuing a particular topic. He suggested that the scientist should weigh up the advantages and disadvantages of his work and make this knowledge known.

When Sir Frederick was talking on the prospects for science in Britain in the 1970s his listeners were possibly most attentive. But with his review of the future of the research councils yet to be published Sir Frederick merely defined the problem. He asked whether research within the universities should keep pace with the expansion in higher education and whether research should be concentrated in "centres of excellence". Sir Frederick did not believe that such centres would involve the risk, as feared by some people, of not producing good scientists from the less favoured institutions provided the present system of both University Grants Committee support and research council support is maintained. He did issue a warning, however, that a shortage of money will possibly require more inter-university collaboration in research.

Sir Frederick also mentioned collaboration between scientists and social scientists. He said that it was almost certain that a much closer relationship must develop between science policy, social economic affairs and government policy but there was no clear way how this relationship is to be achieved.

INDUSTRIAL RELATIONS

Battle or the War?

THE majority ruling of three Appeal Court judges last week means that Mr Jack Hill has won his battle with C. A. Parsons, the Newcastle engineering company who dismissed him for refusing to change his trade union. It remains to be seen, however, whether the United Kingdom Association of Professional Engineers (UKAPE), of which Mr Hill is a member, has won the war.

The appeal was against Mr Justice Brightman's decision earlier this year that under the law as it stands he could

not prevent Parsons from dismissing Mr Hill for refusing to leave UKAPE and join DATA—the Draughtsmen's and Allied Technicians' Association—who, by working to rule twice and striking once, won a closed shop agreement from the company (see *Nature*, 233, 5; 1971). When Mr Hill refused to join DATA, he and thirty-seven other engineers were given a month's notice. Mr Hill sued the company for wrongful dismissal and both he and UKAPE saw the resultant action as a test case.

Not so the company apparently. The day after the appeal decision Mr Kenneth Peplow, the general secretary of UKAPE, said that he had been informed by the company's solicitors that UKAPE will have to fight the remaining cases individually, but at the moment Parsons will not confirm that further action will have to be taken.

If thirty-five more actions are needed (two engineers have left the company since July) then Mr Peplow sees it as "a campaign of spite", but adds that he cannot believe it has been generated by the company. "It makes one wonder," he said last week, "what influences and pressures have been brought to bear so that a company is no longer in control of its own destiny."

Mr Harry Smith, DATA's public relations officer, said this week that they are "disappointed", but he was not prepared to commit himself on what DATA expects of the company until the association had met its legal advisers yesterday and representatives of the company next Tuesday, but they are clearly reluctant to accept last week's ruling as a test case.

Whether it is a test case may prove to be an academic question, however, as any writ issued now is unlikely to be heard before the relevant clauses of the Industrial Relations Act become law early next year. As UKAPE have registered as a trade union under this act, and DATA have deregistered, then it would appear that UKAPE will be in a stronger legal position.

UKAPE's determination to see this through is reflected in its appeal for a defence fund of £1 million launched last week. UKAPE has 11,000 members but is hoping that it can raise £5 a head from the 200,000 engineers in Britain. UKAPE is determined to fight for recognition wherever it is denied, according to Mr Peplow, and the new act could give it the opportunity to do so effectively. Mr Peplow emphasizes that UKAPE is determined to act legally and to adhere to the code of ethics that it maintains is the distinguishing feature between professional associations and trade unions, but it is equally determined to protect what it sees to be its rights. Companies other than Parsons may have to face up to UKAPE soon.

STEEL

Rationalizing Research

THE British Steel Corporation's efforts to rationalize and coordinate the research performed in its own laboratories is coming to fruition, according to a report which surveys the work in progress (*Steelresearch 71*, British Steel Corporation; 1971).

Steelresearch 71 is the first comprehensive annual review of the research activities of the corporation, which now cost about £9 million a year. As well as describing the work of the laboratories attached to the corporation's six product divisions, the report also covers the activities of Bisra which, since 1967, has gradually evolved from an autonomous research association into the corporate laboratories of the British Steel Corporation. The decision that a separate annual report is no longer to be published is a clear sign that the amalgamation of Bisra into the corporation's research structure is now almost complete. Almost 95 per cent of the £2.7 million spent by Bisra comes from the British Steel Corporation and it now has an important role to play as the central body responsible for research of an innovative or long-term nature (for example operational research devoted to increasing the efficiency of all aspects of the corporation).

The corporation's other research activities have centred on the product divisions (for example the special steels division and the tubes division) which themselves evolved from the four groups formed on a geographical basis when the corporation was created in 1967. There has inevitably been wasteful repetition of research and during the past year there have been particular efforts to minimize it. Because of their expertise in on-line non-destructive testing, for example, the laboratories of the tubes division at Corby have assumed special responsibility for the development of these techniques; the Swinden laboratories of the special steels division at Rotherham have, for similar reasons, been designated a centre of expertise in the machinability of steels.

The reorganization of research activities reflects the work of the research committee whose wide ranging brief is to "review and coordinate the research and development work of the divisional and corporate laboratories". A spokesman for the British Steel Corporation said this week that further rationalization along similar lines could be expected when other areas have been identified in which the drawing together of projects would be fruitful.

The corporation also spends £100,000 a year in universities and a further £60,000 a year on about sixteen fellowships, usually tenable for two years.

NEW WORLD

Controlled Optimism for Fusion Power

by our Washington Correspondent

CLEAR signs of optimism for the prospects of producing marketable power from controlled nuclear fusion emerged in Washington last week. Indeed, one expert on the subject even went so far as to declare that "progress towards power through nuclear fusion is now limited by resources available to the programme rather than by scientific obstacles".

Although such unqualified optimism may have been tinged to some extent by the fact that the remarks were addressed to members of the Joint Committee on Atomic Energy—the Congressional body that holds the purse strings for the controlled thermonuclear research project in the United States—a string of witnesses before the committee produced good evidence of progress with which to back up their assertions. Nobody was of course prepared to say that fusion power is just around the corner, but almost every witness before the committee felt confident enough to predict that the feasibility of producing power from nuclear fusion will be demonstrated by the end of the decade.

The logical extension of this optimism is that decisions will soon have to be taken on whether the predictions should be backed by large increases in funds—a situation which in itself demands some potentially painful ordering of priorities within the controlled thermonuclear research programme. But exactly what level of funding is now needed, and in particular how it should be applied, is an open question.

Members of the Joint Committee on Atomic Energy were anxious last week to solicit from their witnesses some idea of how soon power from nuclear fusion would be able to compete economically with power produced by other means. That question, indeed, emerged as the central point of interest to the committee, which was clearly trying to use the advent of marketable fusion power as the base point by which to judge the level at which funding should in future be authorized. Not surprisingly, the committee received a spread of dates, ranging from about 1990 as the most optimistic, given a very high level of funding, to "some time before 2020". The consensus was, however, that it is probably realistic to talk in terms of producing commercial power from fusion plants by the year 2000 although the actual date will depend in very large measure on funding.

The fact that scientists deeply involved in the research programme are now willing to talk, even in vague and handwaving terms, of the possible date of applica-

tion of fusion power, when the feasibility of even producing such power has yet to be demonstrated bears witness to the considerable theoretical advances that have been made during the past few years. Indeed, it can now be safely said that the point will shortly be reached at which very large equipment will be needed to determine whether the advances made in the laboratories hold up on a large scale.

The point was very clearly brought out last week that there are essentially three milestones which must be passed on the road to thermonuclear fusion power. The first is the demonstration of scientific feasibility—the immediate goal towards which present research is directed—then comes the building of a demonstration plant to test whether the processes developed in the laboratory can indeed be applied to energy production, followed by prototype and commercial power plants. For nuclear fission in the United States, the gestation period between proof of scientific feasibility and commercial production was some 25 years, but last week the scientists engaged on the research were predicting that the comparable time lag for fusion could be cut down to about 15 years with sufficient funding.

As for the demonstration of scientific feasibility, the chief objective is to heat a plasma fuelled by deuterium or a mixture of deuterium and tritium to a very high temperature, and confine it in a space free from contact with any material walls long enough for a fraction of the fuel to react. That, in essence, is the required operation, but so far no techniques in the laboratory have come close to containing the plasma long enough, or heating it to the required temperatures. In the United States at least, the chief thrust of the research over the past few years has been directed towards confining the very hot plasma by means of magnetic fields, and it is this research which is now producing the promising results.

Research aimed at finding methods for confining the very hot plasmas has in the past followed four different paths. At the Lawrence Livermore Laboratory and the Oak Ridge National Laboratory, plasma physicists have been studying confinement by so-called magnetic mirror devices, which essentially hold the hot plasma in a specially shaped magnetic field. The problems come when the plasma is sufficiently dense to argue back at the field, and diffuse across it so rapidly that it is confined for too short a time to react. The theoretical understanding of the instabilities

which cause the rapid diffusion has, however, reached such a state that Dr R. F. Post, who is in charge of the project at the Lawrence Laboratory, told the committee last week that "I'm optimistic about the prospects for controlling them . . . if we can in fact demonstrate their control we should be ready for scientific feasibility tests".

Mirror devices, which work with plasmas of relatively low density, need to contain the plasma for a relatively long time to meet the criteria necessary for scientific feasibility—of the order of 1 s. The devices which have made the headlines recently, the tokamaks and stellarators, also employ magnetic fields for confining the very hot plasmas, and work with slightly denser plasmas than the mirror devices. In some respects, the two types of device have similar characteristics, but the tokamaks confine the plasma in a toroid. The chief breakthrough with these machines came in 1969, when a large tokamak in the Soviet Union produced an unexpectedly large heating.

The other two approaches consist of techniques for suddenly compressing a plasma by a magnetic field (the so-called "pinch" machines), and of rapidly heating a solid block of fuel by means of a laser. Proponents of each method for reaching the criteria for achieving power from fusion presented evidence last week to show that they are close to the breakthroughs needed to demonstrate scientific feasibility, and this is one reason why those in charge of planning the controlled thermonuclear research programme in the United States will soon have some difficult choices to make. The problem is that to take any of the methods to the stage of demonstrating feasibility will require the expenditure of large sums of money on big machines, and, sooner or later, one or two of the approaches are bound to fall by the wayside while the others are taken to the next stage. That, of course, would mean a dereliction of ambition in many laboratories.

Another problem for the planners is that reactor designs associated with each of the methods now being investigated would have individual characteristics, and it is therefore a potentially wasteful process to concentrate too much on power plant design, at least until the scientific feasibility stage is almost reached.

All the witnesses last week emphasized, however, that it is still too early to decide which horses to back, and the policy of keeping all options open is the correct one at present. Whether or not

the Joint Committee on Atomic Energy is willing to increase its widely spread bets is, however, a moot point, but it was clear last week that key members of the committee are more ready at present to back the breeder reactor.

PESTICIDES

A Few Loopholes

by our Washington Correspondent

IF a bill passed last week by the House of Representatives finds its way to the statute books, the federal government will for the first time have the power to regulate and control the manufacture and use of pesticides. At present, federal controls on pesticides apply only to their labelling and to their sale across state lines. But the squeals of anguish that might be expected from the chemicals companies and from the powerful farming lobby at such a prospect have been drowned by the protests of environmentalists.

Environmentalists charge, with some justification, that the bill is a toothless shadow of legislation introduced into Congress earlier this year by the Administration, and that it contains some important loopholes for chemicals manufacturers. Spokesmen for the chemical industry are, however, much less willing to comment on the bill except to admit that it will be easier to live with than the Administration's original proposals.

In its present form, the bill establishes the important concept that the Environmental Protection Agency should have the right to inspect manufacturing facilities, which would be registered with the agency, examine records and take samples. And, as far as pesticide use is concerned, the bill requires that all pesticides be registered with the EPA, which would classify them as either for general use or for restricted use. As for enforcement, controls on the manufacture or use of pesticides would be enforced by the states, and the EPA's regulatory arm would be stiffened by powers allowing it to bring court injunctions, impose civil penalties, seize unlawful products or bring criminal charges against violators.

There are also provisions in the bill for public comments on any action taken during registration of a pesticide, or during the proceedings that follow cancellation or suspension of an agent's registration. Questions of scientific fact would be referred to the National Academy of Sciences, in much the same way as under the existing law, but the new bill also allows a scientific review to take place in conjunction with a public hearing, while the existing law separates the two procedures, thereby causing undue delay.

All that, of course, raises few objec-

tions among environmentalists, for it considerably stiffens existing laws, and allows for at least a minimum set of standards to be enforced on the manufacture and use of pesticides. In that respect, it represents a considerable step from the present law which only gives the federal government powers to enforce labelling standards, and to ban or restrict the sale of pesticides between different states. But environmentalists are concerned both by other provisions that found their way into the bill, and by some concessions that chemicals manufacturers managed to wring from the Agriculture committee before it reported the bill to the House.

One bone of contention is that the Administration's original proposals called for the classification of pesticides into three categories, the last one being for use by permit only. This was deleted by the committee on the grounds that it would be too difficult to enforce, and means that some of the most toxic chemicals would instead come under the less rigorous controls imposed on the "restricted use" category in the present bill. Another proposal which has irked critics of the chemicals industry is the provision written into the bill for paying federal money to manufacturers who are left with considerable quantities of pesticide on their hands in the event that a pesticide's registration is cancelled. This provision was bitterly attacked when the bill was debated in the House, on the grounds that the government would effectively be paying industry for its own mistakes. But in the event, an amendment to delete the provision was rejected by a wide margin.

The Agriculture committee also wrote into the bill the provisions for scientific review by committees of the National Academy of Sciences. According to one member of the committee, this provision was put into the bill at the insistence of the Environmental Protection Agency, and the committee held a special session to draft it into the bill. Congressman John Dow, chief spokesman against the bill on the floor of the House, and also a member of the Agriculture committee, insists, however, that such a scientific review can be effectively used by chemicals manufacturers to hold up proceedings, and moved to have the provision deleted from the bill. His amendment was rejected by a voice vote, however. The National Academy of Sciences itself would also have been happy to see its name removed from the bill, since such a provision tends to erode its independence from the government.

All these arguments are likely to have a second showing early next session, when the Senate should be voting on companion legislation. So far, a Senate committee has conducted hearings on

the Administration's bill, but no bill has been sent to the Senate itself.

HEALTH MANPOWER

Plugging the Gap

by our Washington Correspondent

THE House of Representatives last week sent to President Nixon a bill providing \$2,900 million over the next three years for the training of doctors. The bill is the product of protracted negotiations in a conference committee which was set the difficult task of reconciling differences between fundamentally different bills passed in August by the House of Representatives and the Senate. Chief intent of the bill is to increase the numbers of doctors in the United States, particularly in areas where there are substantial shortages.

The bill now awaiting the President's signature, although it involves expenditures considerably in excess of the modest proposals sent to Congress earlier this year by the Administration, is expected to meet with little resistance in the Administration. The bill authorizes construction grants to medical schools, totalling \$225 million in 1972, \$250 million in 1973 and \$275 million in 1975. Medical schools would also receive federal funds on the basis of their student enrolment, with grants of \$2,500 for each student in his first, second and third year, \$4,000 for students in their fourth year, and as an incentive for schools to shorten courses, the bill provides for the schools to receive \$8,500 for every student in the final year of a three-year course.

Another incentive for existing schools to step up their output of medical students is a provision in the bill which seeks to make a substantial grant to colleges which usually provide two-year courses in basic medical science. Such schools that convert to four-year medical schools will, under the terms of the bill, receive grants of \$50,000 multiplied by the numbers of medical students enrolled in their first third year class. As for student support, the bill set aside \$50 million next year, rising to \$60 million in 1974 for loans to students in the health professions.

The House version of the original bill was produced by the Interstate and Foreign commerce subcommittee, under the chairmanship of Paul G. Rogers, while the Senate version was sponsored by Senator Edward M. Kennedy. Both sponsors declared themselves pleased with the conference committee bill, and the final bill received widespread support in both chambers. In the House, where it only collected three opposing votes, only one member was prepared to speak up against it. His chief grievance was that the bill is the first step on the road to socialized medicine.

Short Notes

Alaskan Oil

CONGRESSIONAL aides have hit upon a peculiarly effective technique of bringing controversial suggestions to public attention. It consists of burying them deep in reports almost as though they were not meant to be noticed. A striking demonstration of the effectiveness of the technique was provided last week when a single five-line paragraph in a 100-page report on oil pricing made headlines. The paragraph suggested that there are oil deposits off the southern coast of Alaska that may be as extensive as those on the North Slope, but that the oil companies are not interested in developing them, and that the Department of the Interior is attempting to conceal the extent of the deposits from public view.

Oil companies reacted vigorously to the allegations by suggesting that although there may be oil deposits there, test bores have failed to detect them, and spokesmen for the Department of the Interior have hotly denied the allegations, saying that no preliminary study of the extent of possible deposits in the Gulf of Alaska has yet been made. The Department of the Interior is, however, now studying seismic data it has bought from two oil companies that have surveyed the region. So far, two oil consortia have sunk test bores in the Gulf of Alaska, but both have been abandoned because of damage from heavy seas. One problem with the area is that even if there is oil in any quantity under the gulf, it would be very difficult to extract because of the notoriously bad weather.

House votes Cancer Bill

THE House of Representatives this week passed by a vote of 350 to 5 the bill sponsored by Paul G. Rogers designed to increase the funding for cancer research but to keep it within the National Institutes of Health. The bill now goes to a conference committee where it must be reconciled with a bill passed in July by the Senate designed to set up an independent agency called the Cancer Cure Agency. Although the bills represent a fundamentally different organizational structure for cancer research, both would greatly increase the funding—the House bill calls for \$1,500 million to be spent over the next three years, while the Senate bill asks only for such funding as necessary. Rogers said this week that he is confident the conference committee will agree to keep cancer research in NIH.

Water Pollution

ANY illusions about there being no votes in sewage were quickly shattered last week when it became known that the White House is actively lobbying to have Senator Edmund Muskie's water pollution control bill changed during its passage through the House of Representatives. The bill, which was recently passed by the Senate by a vote of 85-0, calls for a rigorous programme to make all waterways in the United States fit to swim in by the year 1985. A central part of the bill is that responsibility for setting and enforcing water quality standards should be transferred from the states to the federal government. It now seems that the White House is trying to give the states some of their authority back. A re-draft of the Senate bill is said to have been sent out to state governors to enlist their support, and to demonstrate to them the White House's concern for their interests. Another aspect of the bill that has caused concern is its cost both to the government and to private industry, and the prospects of a White House-industry coalition do not augur well for the chances that the bill will remain intact during its passage through the rest of the Congressional mill.

DES

THE tide of opposition to the use of the synthetic hormone diethylstilboestrol in cattle feeds gained considerable strength last week. The hormone, which is used to promote growth in cattle, has been under attack since it was reported in the *New England Journal of Medicine* earlier this year that the mothers of 13 girls who developed an extremely rare cancer of the vagina had taken the drug to prevent miscarriage. Since then, there has been a suit filed in the district court to ban the hormone from cattle feeds, Senator William Proxmire has introduced a bill into the Senate, designed to bring about the same end, and experts of the UN Food and Agriculture Organization have spoken out against its use. The Food and Drug Administration has finally been persuaded to act—last week it proposed a labelling change that would warn doctors not to prescribe the hormone to pregnant women.

While this furore has been going on, however, it has been reported that DES is an effective contraceptive agent if taken within 72 hours of intercourse.

AEC

THE Atomic Energy Commission's new regulatory procedures and its new-found attention to environmental and safety factors outlined recently by its chairman James R. Schlesinger, are causing administrative upheavals within the AEC. Chief changes are the creation of a new deputy directorship for reactor

licensing and the temporary drafting of 30 professional staff to the regulatory division from other parts of the agency. The AEC is now busy sorting through all the petitions from the power industry showing why their plants should not be shut down or construction stopped, while an environmental review takes place.

New Head for NSF

THE nomination of Dr H. Guyford Stever as director of the National Science Foundation, announced this week by President Nixon, brings to the NSF a man who is well versed in the workings of Washington's scientific establishment. Dr Stever, who will succeed Dr William D. McElroy as director of the NSF on February 1, 1972, is a member of the National Science Board and the advisory panel to the House of Representatives Subcommittee on Science and Astronautics. He has also been Chief Scientist to the Air Force, Chairman of the President's Commission on Patent Systems and a member of several federal scientific advisory committees on science and astronautics. Dr Stever is now president of Carnegie Mellon University, a position he has held for the past six years.

A physicist by training, Dr Stever is an expert on aeronautical and space engineering. He received his AB degree from Colgate University and his PhD from California Institute of Technology and was a member of the Faculty of MIT for 20 years before his appointment as president of Carnegie Mellon University. Between 1942 and 1945 he served in the Office of Scientific Research and Development in London. During his time at Carnegie Mellon University, the establishment has undergone some substantial changes including the merger between Carnegie Tech and Mellon Institute which formed the basis of the present university, and it was also one of the first institutions to receive an NSF science development grant.

Dr Stever comes to the foundation at a critical time in its history. For one thing the past year has seen a tug of war between the Administration and Congress over the NSF's programme of research applied to national needs and its support of graduate education. Although the relative funding for the programmes will be worked out during Dr McElroy's directorship, Dr Stever must justify the foundation's budget to Congress next year.

NEWS AND VIEWS

Plutonium-244 on the Earth

ONE of the most fascinating detective stories in the history of cosmological and cosmogonical science seems to be solved with the publication in this issue of *Nature* (page 132) of the discovery of plutonium-244 in nature. A joint team of scientists from the Los Alamos Scientific Laboratory and the General Electric Company discovered the elusive nucleus in an old Precambrian rare-earth mineral called bastnasite. Everybody had suspected the natural existence of ^{244}Pu by the clues it had left from the early days of the solar system, and now it has actually been found.

The clues in this mystery began accumulating in 1960 when Kuroda suggested that the excess xenon gas isotopes ^{131}Xe , ^{132}Xe , ^{134}Xe , and ^{136}Xe , which he had found in the achondritic meteorite Pasamonte, had resulted from the spontaneous fission of some heavy radioactive nucleus that had a sufficiently long half-life to have been incorporated into the meteorites when the solar system formed and to have remained there until the meteorites cooled and solidified, enabling them to trap the noble-gas fission fragments. Kuroda specifically suggested ^{244}Pu , which has a half-life of 82×10^6 years. Other workers were also able to find a reproducible spectrum of fission-like xenon in other achondrites, where the low concentration of xenon arising from other sources (primaevial xenon) and the high concentrations of uranium, which chemically accompanies Pu, presented favourable circumstances for the detection of this xenon component.

Then two years ago an exceptionally high concentration of this same isotopic pattern of xenon isotopes was found in the uranium-rich mineral whitlockite, from the St Severin chondritic meteorite. The exciting new clue in this case was that this same whitlockite mineral showed, upon etching, an excess of fission tracks; however, it still could not be argued that the fissioning culprit was ^{244}Pu .

A nagging problem throughout these investigations had been that the yields of xenon isotopes in ^{244}Pu fission had never been experimentally determined because of the difficulty in assembling a large enough sample of ^{244}Pu . Thus the mysterious isotope ratio observed reproducibly in meteorites, $^{131}\text{Xe} : ^{132}\text{Xe} : ^{134}\text{Xe} : ^{136}\text{Xe} = 25 : 88 : 92 : 100$, could not with certainty be attributed to ^{244}Pu . Recognizing the importance of these ratios, a team from the Oak Ridge National Laboratory electromagnetically separated 13 mg of ^{244}Pu from large quantities of neutron-irradiated plutonium. After a 23-month wait to allow sufficient ^{244}Pu fission, a Berkeley team confirmed these fission isotopic ratios directly (*Science*, **172**, 837; 1971). This was the final clue that proved that ^{244}Pu existed in the solar system when the meteorites formed. It only remained to detect its small residues in some object today.

The difficulty in finding natural ^{244}Pu is that the solar system formed about 60 half-lives ago, so that the average concentration of ^{244}Pu should be only about $(\frac{1}{2})^{60}$ of its

concentration when the meteorites formed! Inasmuch as an upper limit to that absolute concentration would be expected to be only 3×10^{-25} g per gram of earth even if ^{244}Pu were originally as abundant as ^{232}Th , surely an overestimate by a factor near 100, it was clear that the search must be made in some mineral that would have, in the long and complicated chemical history of the Earth, concentrated the plutonium.

Because the chemistry of Pu is similar to the rare earth Ce, the Los Alamos group studied a large inventory of the extractant used by the Molybdenum Corporation of America to purify Ce from old bastnasite ores. The Ce is almost 10^6 times more concentrated in this mineral than its average concentration; and, sure enough, the long sought ^{244}Pu was there too. Although the chemical enrichment of Pu would have to be about 10^8 (that is, about 100 times more concentrated than Ce) above the ^{244}Pu abundance of 7×10^{-27} g/g expected from the meteoritic concentrations of fission xenon, the results seem convincing. With this discovery, ^{244}Pu leaves the category of "extinct radioactivities" and joins ^{235}U in the category of "almost extinct radioactivities".

The cosmological significance of these discoveries is both simple and profound. When the primaevial meteoritic abundance of ^{244}Pu is considered in conjunction with that of ^{129}I , an extinct radioactive species that decays to ^{129}Xe leaving a different xenon anomaly in the meteorites, it can be concluded that about 1.8×10^8 years elapsed from the time when a portion of interstellar gas collapsed into the gas cloud that was to form the solar system and the time when the newly formed meteorites were cool enough to retain noble xenon gas. This well determined interval for the formation and cooling of the meteorites poses a firm challenge to theories of the formation of solid objects. But the implications do not stop there. Because ^{244}Pu , ^{236}U , ^{235}U , and ^{232}Th are all synthesized in comparable amounts in exploding objects, their relative abundances reveal that nucleosynthesis began in the galaxy about $12 \pm 2 \times 10^9$ years ago and occurred continuously from that time until the time the solar system formed about 4.7×10^9 years ago. This age pattern for galaxies must now be regarded as a prime fact for cosmology.

There is, however, another possible interpretation of the Los Alamos discovery. The Los Alamos group acknowledge that heavy cosmic rays may bombard the Earth with a flux such that the average terrestrial concentration of ^{244}Pu would be about 5×10^{-25} g/g. But because the Precambrian bastnasite is, as a mineral deposit, older than 5×10^8 years, the ^{244}Pu concentration would now be only about 5×10^{-27} g/g if it had been deposited on the Precambrian Earth by cosmic rays. They suggest that the detection of natural ^{244}Pu in younger minerals can illuminate this possibility. Thus an intriguing cloud of uncertainty still surrounds their remarkable discovery.

PLATE TECTONICS

Ancient Plate Motions

from our Structural Geology Correspondent

ONE of the problems facing the structural geologist is that of determining the net displacement related to crustal shortening across an orogenic fold belt; indeed, it is often difficult to determine even the orientation of displacement vectors giving the direction in which the opposing edges of the belt have moved. Most orogenic zones have their constituent fold and thrust structures developed parallel to the gross linear trend of the belt and it is this conformity that has led most structural geologists to assume that the fold belts have been developed as the result of direct orthogonal closing of the margins, rather in the fashion of the closing jaws of a vice.

The theory of plate motion makes this situation the exception rather than the rule, for only in extreme conditions will the relative motion of colliding plates have occurred perpendicular to the plate margins. W. B. Harland (*Geol. Mag.*, **108**, 27; 1971) has formulated a range of deformation situations which can be developed as a result of varying relationships between the direction of plate motion and the attitude of the plate edge. In this analysis the traditional regimes of extension, transcurrent and compression occur only as the result of special orthogonal relationships between moving plates.

For the general motion of plates Harland recognizes two novel regimes: transtensive regimes operating in zones of oblique extension, and transpressive regimes in zones of oblique compression. The former is typified by the opening of the Atlantic Ocean where the spreading ridge is repeatedly offset by transform faults, whilst it is the latter that is particularly pertinent to the present discussion.

During the early stages of deformation, fold and thrust structures will tend to develop perpendicular to the motion of the colliding plates and hence oblique to the plate margins. If the structures were to be frozen at this stage there would be no difficulty in recognizing both the transpressive nature of the deformation and the direction of motion of the associated plates. As the two plates continue to move, however, one plate sinks beneath the other and so these early structures are increasingly transpressed, the fold axes and thrusts being gradually rotated into alignment with the plate margins. The effects of transpression can, therefore, be divided into two distinct stages: first, a component of compression with shortening parallel to the plate motion and, second, a component of transcurrent with extension parallel to the plate margins.

The various manifestations of the extension component outlined by Harland

are not by any means always easy to recognize and this factor has largely contributed to the false impression that most fold belts have been developed by orthogonal compression. Some measure of the direction of plate motion can be reached by virtue of the fact that the smaller the angle between the plate margin and the direction of plate motion the greater the component of transcurrent. But it is unlikely that even detailed strain analysis of a fold belt would lead to any precise assessment of the displacement vector, as normally the strain will be heterogeneous throughout the belt.

A. G. Smith (*Bull. Geol. Soc. Amer.*, **82**, 2039; 1971) has suggested a far more compelling model to determine ancient plate motion. Smith's reasoning is based first on the fact that, in recent oceans, plate motion is parallel to transform faults and perpendicular to spreading ridges and, second, on the contention that it is possible to reconstruct ancient plate margins—and hence plate motions—by restoring the past

positions of fold belts, transforms and spreading axes. Clearly, the reliability of the restoration of the plate margin will decrease with age, but Smith has been able to reconstruct the relative positions of the continental areas surrounding the Mediterranean by means of a computer match of the continental margins which he showed to be consistent with a three stage model for the opening of the Atlantic.

The model demonstrated the existence by Lower Jurassic time of an extensive Tethys Ocean, entirely east of and separate from the present Mediterranean, which was gradually and completely closed during the three distinct movement phases associated with the opening Atlantic. Smith postulates that the Great and Little Caucasus Mountains represent transpressive fold belts developed by the closing of the Tethys; the former along the northern margin with Laurasia and the latter along the southern margin with Gondwanaland. The west to east plate motions involved can be determined from the N-

Palaeozoic Movement in the Iberian Peninsula

THE geological structure of central and southern Europe is dominated by features formed during two collisions between continents. The first of these occurred before the Atlantic was formed when a land mass extending from present-day North America into northern Europe impinged on north-west Africa and an extensive mountain system formed in central and southern Europe. These movements ended about 225 million years ago and were followed about 200 million years later by a collision between Africa and southern Europe which occurred as the Atlantic opened and the Tethys Sea, which lay along the southern flank of Europe, finally closed.

Understanding the structures formed in the earlier of these collisions is particularly difficult because the Hercynian fold belts formed at that time were disrupted by the more recent movements and over much of Europe have been buried by younger deposits. In the past few years it has become clear that the most recent approach of Africa and Europe was accompanied by several subsidiary displacements as smaller blocks of crust were rotated or squeezed between the colliding continents. The rotation of Spain and Portugal, first postulated by Carey, is one instance in point. The reality of this rotation has been substantiated by palaeomagnetic measurements within the Iberian Peninsula and by evidence obtained on the floor of the Bay of Biscay which indicates that the bay developed as France and Spain separated. But it is still far from clear how the various

smaller blocks, displaced during the Alpine movements, were originally situated. Analysis of contemporary earthquakes indicates the sense of movement of the smaller plates of crust at present, but earlier movements have to be inferred by other means.

An article by Ries and Shackleton in next Monday's *Nature Physical Science* bears in two ways on this problem. The article presents a new synthesis of Palaeozoic structures preserved in north-west Spain and northern Portugal. It thus provides direct evidence of the possible nature of Hercynian movements in this part of the Palaeozoic fold belt. But the structures recognized by Ries and Shackleton are so large that it seems possible that they once continued outside Spain and Portugal and so may, in the future, be used to reconstruct the relationships as they existed before later movements opened the Bay of Biscay. The structures are complex; the critical new point is the recognition by Ries and Shackleton that several isolated masses of Precambrian rock now found above younger strata once formed part of a thrust mass of crystalline rock. They suggest that this formed a plate of continental crust driven from a westerly source, presumably as a result of a Palaeozoic collision of continents. If their tentative synthesis is supported and can be extended into other parts of the Hercynian chain, the results of Ries and Shackleton may also throw light on the nature of the much younger movements which disrupted south-west Europe in Tertiary times.

S attitude of the restored Lower Jurassic spreading ridge, remnants of which are found in the ophiolite sequences of Yugoslavia and Albania, and the E-W transform between Spain and North Africa.

Powerful as this method is in unravelling the complex plate motions involved in the Alpine Orogeny, we have as yet completely inadequate data for it to be used in connexion with the older orogenic belts.

SELENOLOGY

Astronauts in Britain

by our Astronomy Correspondent

BRITAIN'S tight-knit lunar and planetary science community last week had more opportunities than usual for getting together. On Monday morning nearly two dozen lunar scientists gathered at Cambridge for a private session with the Apollo 15 astronauts, most of them later hot-footing to London for an afternoon meeting of the Royal Society discussion group on lunar and planetary sciences. On Friday many of them were back in London again, this time for a discussion on the temperature regime within the Moon, the first of this season's specialist meetings of the Royal Astronomical Society which have become such a success since their introduction last year.

Of the three meetings, that at the Royal Society was the most significant. Attended also by Mr J. Smith and Mr J. Hosie of the Natural Environment Research Council and the Science Research Council respectively, the chief sources of support for British lunar and planetary sciences, the meeting included a review of the programmes that are under way and the prospects for the future. One interpretation of the outcome of the meeting was that the research councils could offer little hope of a diversion of funds to the lunar and planetary sciences in the foreseeable future.

Earlier in the day the dialogue with the Apollo 15 astronauts uncovered no information that had not already been revealed by Houston. Nevertheless the way in which the meeting developed, with attention centring on what might be termed lunar stratigraphy, suggested that in future the factors that have resulted in the morphology of the lunar surface may soon be receiving as much attention as the petrology of the lunar samples has up to now.

Colonel David Scott and Colonel James Irwin, who made up the Apollo 15 landing party, were lucky in being the first to visit an area of the Moon having a rich landscape. But they were unable to throw any light from their personal observations on the origin of

the Hadley rille, the most striking feature in the landing area. There were certainly no markings on the floor of the 400 m deep rille that indicated to the astronauts how it might have been formed. But Scott reported that the rille appeared to cut through a well-defined unit of rock—visible on the wall of the rille opposite the landing site—that appeared to contain between eight and twelve sublayers in a thickness of eight metres. Although photographs from orbit have indicated that some other rilles show fairly well-defined shelves, Hadley rille was not previously known to contain such a feature. There was some discussion at the meeting about whether the sublayers represent separate flows of lava or differentiation within a single unit.

Markings on a large scale were prominent on several of the hills around the landing site. In particular the visible face of Mount Hadley has a grid of subhorizontal striations which are crossed by another grid of more steeply dipping markings. There seems to be a possibility that one set of markings represents fracturing in the rock, this pattern interacting with erosion of the surface material of the mountain to generate the second set of markings.

Apollo 15 was of course the first of the J series of missions carrying instrumentation that is more sophisticated than was possible on the early pathfinding flights. In particular the addition of the lunar rover allowed the astronauts to cover four times the distance that was possible for the crews of Apollos 11, 12 and 14 and to collect 78 kg of samples, compared with only 98 kg from the three previous missions put together. Colonel Alfred Worden, who was responsible for the command module while his colleagues were on the lunar surface, reported that the high

precision mapping cameras that were carried for the first time on Apollo 15 were used to cover about eight per cent of the front surface of the Moon. From photographs taken from orbit of the landing craft with the lunar rover parked beside it, Worden estimated the mapping camera to have a resolution of better than 1 m. No doubt the output from the mapping camera will be valuable in the choice of a landing site for Apollo 17, the last of the Apollo missions in the foreseeable future.

The experiments left behind on the surface also seem to be functioning as anticipated; in particular the seismometer at last completes the triangle of stations that the lunar seismologists need to pinpoint the epicentres of moonquakes. One source that demonstrates activity associated with the perigee of the Moon's orbit around the Earth was reported to have been located to the south of the Apollo 12 and 14 landing sites.

Colonel Irwin also reported what amounted to a road test of the rover. It reached a maximum speed of 13 km hr⁻¹, well in excess of the expected maximum of 9.3 km hr⁻¹, and in fact he and Colonel Scott were able to average 9.6 km hr⁻¹. In spite of the initial difficulty the rover had a responsive steering, and Irwin was surprised at how well it climbed slopes where the dust layer was deep enough to make walking difficult.

The meeting at the Royal Astronomical Society, which had Professor Raymond Hide as chairman, was concerned with the temperature structure of the Moon. The approach taken by several speakers was to point out the limits on the thermal history of the Moon that can be set from different types of measurement.

Variability of OJ 287

THE way in which radiation from a quasar in different parts of the electromagnetic spectrum is related to one common source—if it is related to a common source at all—remains a mystery. One of the best ways to investigate such a relation is to study fluctuations at different wavelengths in the same source; recently, BL Lac, a possible quasar, has been studied in this way. Now, H. M. Dyck and his colleagues have studied the source OJ 287 in the 0.36 to 3.4 μ m range, hoping to relate their observations to those at radio frequencies and in the optical part of the spectrum. In next Monday's *Nature Physical Science* Dyck *et al.* report observations carried out in September and October 1971 in order to determine the photographic

magnitudes of the source.

These observations are suggestive of a power law spectrum with index close to one, consistent with other observations of quasars but rather flatter than the spectrum of the known large amplitude variable sources. It seems that OJ 287 is bright enough in the infrared for sufficiently accurate measurements to provide useful comparison with simultaneous observations at optical and radio wavelengths. In order to be useful, such observations must, of course, be carried out simultaneously, and Dyck *et al.* plan to make further photographic observations from January 3 to 26, 1972, when they hope that other observers will cooperate in a programme of observation at different wavelengths.

PATTERN RECOGNITION

Legs and Beaks

from our Animal Behaviour Correspondent

THE problem of how animals recognize patterns of stimulation from their environments is complex and difficult, particularly where apparently similar stimuli elicit two different responses. Finding the physiological basis for such pattern recognition is of considerable interest. Electro-physiological investigations of the visual system of the cat by D. H. Hubel and T. N. Wiesel (*J. Physiol.*, **148**, 574; 1959) revealed the presence of units specifically responsive to vertical dark bars. Hubel and Wiesel subsequently found (*J. Neurophysiol.*, **28**, 229; 1965) other cells in the cortex of the cat which respond to a slit or bar, but only if it is of limited length. These they called "lower order hypercomplex" cells. Recently, J. P. Hailman has used behavioural evidence to infer that the visual system of a gull chick contains units at least as highly organized as these hypercomplex cells (*Anim. Behav.*, **19**, 328; 1971).

A newly-hatched laughing gull chick (*Larus atricilla*) will peck at its parent's down-pointing, reddish beak and this induces the parent to regurgitate food. In spite of the fact that the legs of the parent gull provide all the known relevant stimulus characteristics (size, shape, colour, orientation) that elicit the beak pecking response, even newly hatched chicks are able to discriminate legs from beak. They only rarely peck at their parent's legs.

Hailman found that a rod or stripe held vertically in front of the chick so that it projected from above and stopped in the centre of the chick's visual field (as would a beak) would be readily pecked by a chick. A chick was much less likely to peck at a rod or stripe projecting vertically upwards from the floor and ending in the centre of the visual field (about where the legs would join the parent's body). This provided a clue as to how the chick was discriminating between leg and beak.

Hailman at first thought that the visual system of the chick contained nothing more complicated than units detecting vertical bars, that is, units which respond to the presence of vertical bars however long or short the bars might be. If more of these units were connected to the upper half of the retina than were connected to the lower half, this would explain why the "beak" stimulus was more attractive than the "leg" stimulus, as the rod pointing downwards from above would excite more of these units than the rod pointing upwards from below. But a long vertical stripe which cut across the whole of the chick's visual field ought, in these circumstances, to be an even better stimulus, as it would stimulate

more of the retina than either of the half-bars.

This expectation was not confirmed. The full-stripe stimulus elicited less pecking than the downward pointing half-stripe (the "beak"). This means that there must be some cells which integrate information from different parts of the retina and respond only when there is a dark vertical bar in the upper portion of the retina and not such a bar in the lower half. They detect not just vertical bars in certain places, but their absence from other positions as well. Such an operation is similar in complexity to that performed by the cat's cortical cells described by Hubel and Wiesel. The search for the units responsible for the gull chick's perception can begin in the knowledge that the perception is organized in a fashion at least as complex as the hypercomplex units of the cat.

LIPID MEMBRANES

Nervous Hysteresis

from our Membrane Correspondent

MORE than thirty years ago the lipid bilayer was put forward by Danielli as an important structural element in biological membranes. Interest in the role of membrane lipids has since fluctuated but is currently very strong and one of the recent areas of activity concerns the role of lipid phase transitions.

In the past few years a battery of physical methods (X-ray diffraction, nuclear magnetic resonance, differential thermal analysis and the like) has been brought to bear on the subject of phase transitions in phospholipid-water systems and most of the emphasis has been

on the so-called melting of the phospholipid hydrocarbon chains in lamellar lipid arrays (bilayers). Over some narrow temperature range characteristic of the particular phospholipid there is usually a transition in the configuration of the hydrocarbon chains from a relatively rigid structure, like that in solid hydrocarbons, to a much more fluid state. This fluid state presents less of a barrier to permeating molecules and ions and is thus the state in which the lipid bilayers would be expected in functioning cell membranes. This expectation was borne out in some recent work of G. B. Ashe and J. M. Steim (*Biochim. Biophys. Acta*, **233**, 810; 1971), who showed that for growth of bacteria to occur it was necessary for the membrane lipids to be in this fluid state.

Attached to their hydrocarbon tails phospholipid molecules also, of course, have hydrophilic head groups. How these head groups might behave at transition temperatures has often been only a matter of passing comment but they evidently also undergo some change in spacing and configuration. How they might do this and its implications in biological membranes is the subject of a recent report by H. Träuble (*Naturwissenschaften*, **58**, 277; 1971).

Träuble used the popular fluorescent probe 1-anilino-8-naphthalene sulphonate (ANS) to investigate the model membrane system in aqueous dispersions of dipalmitoyl phosphatidyl choline (lecithin) which undergo a phase change in the temperature range 40–46° C. Träuble showed that the ANS was intercalated between the head groups at the surface of the lecithin bilayers and the increase in fluorescence which he

Cellular Ribosomes in Arenoviruses

THERE are so many well documented examples of viruses which contain cellular enzymes and/or nucleic acids that Pedersen's claim to have detected ribosomes in lymphocytic choriomeningitis virus particles is not perhaps all that surprising. Electron micrographs of this virus and its relatives reveal within the virions sand-like or ribosome-like granules, from which the group gets its name, the arenaviruses. Pedersen, as he reports in *Nature New Biology* next Wednesday, set about characterizing the RNA species in lymphocytic choriomeningitis virus (LCM virus) in an attempt to establish that these granules are ribosomes. His results substantiate this idea.

The viral RNA is resolved by gel electrophoresis into four components, two of which co-electrophorese with the two cellular ribosomal RNAs. Viruses grown in cells exposed to low doses of actinomycin D, which inhibit ribosomal

RNA synthesis, lack these two species of RNA. The two remaining species, presumably authentic LCM virus genomic RNAs, sediment in sucrose gradients at 23S and 31S and probably have molecular weights of about 1.1×10^6 and 2.1×10^6 respectively.

Because the two putative ribosomal RNAs in LCM virus particles account for about 50 per cent of the total RNA and because treatment of the intact virions with ribonuclease does not eliminate these two RNA species, Pedersen is confident that they are not simply contaminants adsorbed to the surface of the virus particles. In short, the granules seen in electron micrographs of the arenaviruses are almost certainly ribosomes which are presumably engulfed into the virions as they bud from the surface of infected cells, electron micrographs of which reveal accumulations of ribosomes at the site of progeny virus formation.

observed with temperature was attributable to the increased number of binding sites for ANS which were available at the higher temperature. Thus there was evidently a change in head-group configuration with temperature. A comparison of the enthalpy change for the head-group transition, which was calculated from the Van't Hoff equation with published values for the whole process (involving heads and tails), led to the conclusion that the transition is a cooperative process. The "cooperativity factor" (σ) was of the same order as that found for the helix-coil transition of polyglutamic acid. This large degree of cooperativity may be thought of as the nucleation of a two-dimensional "crystallization" of the head groups on cooling.

Changing the pH or calcium concentration was shown to alter or initiate the phase change and it was also shown that in the presence of multivalent ions and also, interestingly, of acetylcholine, the system exhibited hysteresis. Hysteresis means that a given state of a system depends on its past history and thus the system is, in a sense, capable of information storage. Such a hysteresis is also capable of giving rise to oscillatory fluxes in membranes. Träuble also used the temperature-jump method to investigate the rate of the phase change and found that the relaxation time could be markedly reduced by the presence of cholesterol in the lipid phase. With calcium in the aqueous solution as well, the relaxation time was further reduced to the order of 1 ms, which is getting down towards the duration of a nerve impulse. This effect of cholesterol implies a new role for it in biological membranes—that it enables the membrane lipids to undergo a rapid phase change.

These lipid phase changes may be important in the function of the membranes of temperature receptors. Whether such processes are of any relevance in the function of nerve cells remains at present no more than an interesting speculation.

RNA PHAGES

Progeny Release

from our Cell Biology Correspondent

WE know more about the biology of R17, Q β and the other RNA phages—the simplest known phages—than any other group of viruses. The three genes which comprise their genome have been mapped and their functions defined, and two of the proteins specified by these genes have been sequenced. Large segments of the RNA of these viruses have been sequenced and it cannot be long before the entire sequence of the R17 or Q β genome has been elucidated.

The replicase of phage Q β has been isolated pure and used to replicate the Q β genome *in vitro*. Phage particles have been assembled *in vitro* from coat protein, assembly protein and RNA, and the strategy of the viral replication, the way in which ribosomes, coat protein and replicase compete for the viral RNA has been worked out. With so much already under their belts, molecular biologists might be forgiven for regarding the RNA phages as a field of research with nothing much of interest left to be discovered. While it is true that what remains to be found is perhaps unlikely to be as exciting as that found already, the results of recent work by Engelberg and Soudry (*J. Virology*, 8, 257; 1971) and Passent and Kaesberg (*ibid.*, 286) justify their persistence with these phages.

Engelberg and Soudry have tackled the problem of the release of progeny Q β phages from infected cells; a process which does not involve a lysozyme-like enzyme specified by the phage. At 37° C infected *E. coli* lyse, whereas at 30° C infected cells liberate progeny Q β particles without being lysed. This non-lytic release is reminiscent of the release of the filamentous DNA male specific phages, first discovered by Hoffman *et al.* working with MS2, and suggests that the host contributes to the release mechanism. Engelberg and Soudry have now obtained direct evidence that this is the case by using chloramphenicol and rifampin to inhibit host protein and RNA synthesis, respectively. Both

these drugs inhibit the release of progeny phage irrespective of the temperature at which the cells are cultured. Inhibition is not immediate but occurs within about 15 minutes at 37° C and 30 minutes at 30° C, suggesting that a labile host protein is involved. Further evidence for this conclusion comes from the finding that rifampin does not inhibit the release of Q β from infected, mutant cells which are resistant to the drug because they contain a rifampin resistant DNA dependent RNA polymerase (DNA transcriptase). Such resistant mutants continue to make messenger RNA in the presence of rifampin, and also to release Q β . Engelberg and Soudry reasonably conclude, therefore, that a protein specified by a host cell gene is required for continued release of this phage. Short lived protein appendages of male bacteria, the F pili, are the obvious candidates for the release protein.

Passent and Kaesberg have found that in the presence of rifampin, progeny Q β particles are not released because, they postulate, particles are not assembled. Their experiments show that in the presence of rifampin Q β RNA is replicated normally, coat protein is made in almost the same amounts as in the drug's absence (as is the assembly protein) but the yield of phage particles is decreased by about 95 per cent. When resistant *E. coli* are used, the yield is unaffected by the drug. Rather than invoke some failure in a release mechanism, Passent and

Brain and Brawn

THE fine microfilaments which so abound in nerve cells and are particularly prominent near the tips of growing axons are made of actin or, to be more precise, of a protein with striking chemical similarity to muscle actin. That is the remarkable conclusion drawn by Fine and Bray from a series of elegant experiments reported in next Wednesday's *Nature New Biology*. They have isolated the two chief proteins from neurones taken from chick sympathetic ganglia and maintained in culture. These two proteins each account for about 20 per cent of the total protein and one, with a molecular weight of about 55,000, is tubulin, the subunit protein of microtubules. The second major protein, which has a molecular weight of about 45,000, co-purifies and co-electrophoreses on SDS acrylamide gels with muscle actin.

Fingerprints of this protein labelled with 35S methionine can be almost completely superimposed on fingerprints of chick breast muscle actin. The two fingerprints are not completely identical, however, and so at this stage there remains the possibility that the neurone

actin is not identical to muscle actin but the two proteins cannot differ by very much, if at all.

As Fine and Bray comment, it is not perhaps particularly surprising that nerve cells contain large amounts of actin, for axons grow at rates as high as 50 μ m per hour and the tip of the growing axon continually undulates and such motility presumably demands some form of contractile apparatus. They have also obtained evidence which indicates that actin or an actin like protein is in chick embryo lens, lung, skin, heart, pancreas and kidney cells. Furthermore, fingerprints of chick embryo brain actin are so similar to those of muscle actin that the two proteins may well be identical although, as Fine and Bray say, "nothing short of the total amino-acid sequences of the two proteins will establish complete identity".

It seems therefore that actin may be universal to all cells at some stage in their development, the intracellular location and precise function of the protein being in part determined by the other proteins with which it interacts.

Kaeseberg postulate that rifampicin blocks the synthesis of some host factor required for the assembly of the phage. It should, of course, be possible to test this idea by examining cells infected in the presence of rifampin, either by electron microscopy or by a bioassay of homogenates, for progeny phage particles.

POLYNUCLEOTIDES

Base Behaviour

from our Molecular Biology Correspondent

IN the current issue of *Biopolymers* are to be found a group of papers which look deeply into the secrets of nucleic acid structure. Of late, a dispute has centred on the nature of the simplest polynucleotide form, the unpaired unstacked chain. This was viewed, according to disposition, as a rather stiff random coil with a degree of articulation determined by the torsional angles of the backbone bonds, or as a residually stacked structure in which adjacent bases tend to oscillate in parallel planes. Felsenfeld and his colleagues examined poly A (which by optical criteria is substantially stacked) and poly U, the optical properties of which give no evidence of any interactions between bases, and showed that under ideal solution conditions (θ -point) the latter fulfils all the criteria of random coil behaviour. Poly A by contrast is much more rigid, tending to a rod-like condition at low temperature. At high temperatures, however, the structure melts, and approaches the same hydrodynamic state as poly U.

Achter and Felsenfeld (*Biopolymers*, 10, 1625; 1971) have now driven this lesson home by a similar examination of the hydrodynamic character of apurinic acid, prepared by Chargaff's procedure of acid hydrolysis of DNA. The resulting preparation has lost about half the bases, and is therefore, one supposes, essentially devoid of inter-base interactions (especially since these tend to be dominated by purines rather than pyrimidines). The frictional coefficient, as determined from the sedimentation coefficient and molecular weight of each preparation, gives, under the conditions of ideality, the unperturbed coil dimensions. The characteristic function which is normally used to describe the flexibility of the chain comes out for apurinic acid in remarkable agreement with its value for poly U, as well as poly A at 100° C. Achter and Felsenfeld now argue that, were there indeed any optically invisible interactions between bases in an apparently unstacked chain, such as poly U, then apurinic acid, in which on average three-quarters of the surviving pyrimidines are flanked by residues with no base, should have much more compact

coil dimensions. This is not the case; moreover, the similarity between this deoxyribopolymer and the polyribo U seems, as an additional bonus, to destroy an earlier hypothesis—a backbone interaction involving the 2'-hydroxyl group of ribose and the phosphate group—as a significant cause of rigidity in ribopolymers.

There appears never to have been any question but that the stacking tendency is a property of planar π -electron systems, as in the nucleotide bases or polynuclear aromatic derivatives, such as acridines and other stacking dyes. Now Formoso and Tinoco (*ibid.*, 1533) have come up with the singular observation that stacking in dimers may persist when the aromaticity of one of the partners has been destroyed—a situation rather reminiscent of the Buddhist proposition concerning the clapping of one hand. Uracil is readily reduced by a photochemical process to the saturated dihydrouacil. Reduction of this species in the dark, moreover, yields the open-chain derivative, ureidopropionic acid. Formoso and Tinoco have examined the optical properties of a series of dimers containing uridine before and after these treatments. The most striking result was for the reduced analogue of UpA, which shows considerable hypochromicity, and circular dichroism, differing in shape and sign from that of the mixture of monomers. A strange aspect is that whatever interaction causes these perturbations is not liable to thermal melting.

In the ureidopropionic acid derivative, the effect is much greater and is broken down by methanol, though again not by heating. In the dihydro-analogues of UpA and GpU, the manifestations of interaction are smaller, but nonetheless

noticeable, and become more pronounced when the ring is broken. The physical and spectroscopic bases of these phenomena are as obscure as the effects are unexpected. Formoso and Tinoco do not dwell on them, but suggest that they may be of conformational importance in tRNA, where dihydrouridylic acid is found.

In the same issue Davies and Davidson (*ibid.*, 1455) have extended studies of the attachment of monomeric nucleosides to single stranded polynucleotides. The binding is cooperative, and can be presumed to include an important energetic contribution from the stacking of the monomers on the polymer. In none of the combinations that have been studied is the stoichiometry of the association anything other than 2:1 in favour of the polymer. This, Davies and Davidson find, is the case even for the interaction of monomers with copolymers, such as poly UC and poly AC.

Maurizot, Blicharski and Brahms (*ibid.*, 1429) have concerned themselves with the differences in behaviour of ribo- and deoxyribopolymers, and have studied in the first place the formation of double helices by oligomers. They find that both self-association of poly C and poly A under acid conditions, and pairing of poly A and poly U (or poly T), occur much more readily—that is at shorter chain lengths—in the deoxyribo than in the ribo series. Even trimers of dA and dT will give base-paired complexes, whereas chains of rU and rA shorter than seven residues do not associate. These stability differences must be expected to have implications for replication and transcription and the interaction of DNA and RNA with enzymes in general.

Ingredient Y

ONE of the interesting current problems in nucleic acid biochemistry is to find a function for the minor nucleotides present in transfer RNA. It is known that some of them are in themselves cytokinins, or growth factors in plants, but it is by no means obvious why they should appear in tRNA. One of the most unusual structures is that of the so-called Y-base, which occurs in phenylalanine tRNA. It is noteworthy for its strong fluorescence, and this property has been widely used for the estimation of distances between the anticodon loop, where the base occurs, and the chain termini, to which other fluorescent groups can be chemically attached, and also for observation of interactions of the tRNA with other molecular species. Last year the structure of the Y base from yeast tRNA was determined by a group working at Columbia University, and has a strange

structure, the purine being converted to a derivative in which two amino groups in adjacent positions on the six-membered ring form part of a third aromatic ring.

In next week's *Nature New Biology*, Nakanishi *et al.* report the structures of the corresponding base from several mammalian species, which, chromatographic and other evidence suggests, are identical also with the Y base from wheat germ phenylalanine tRNA. The structure for the analogous base from beef, calf and chicken liver, established by degradation and mass spectrometry, resembles that of the yeast Y base, but contains a peroxide group in a ring-substituent chain. This is a remarkable and unexpected compound to be found in a cell. In rat liver the phenylalanine tRNA contains a mixture of the Y base, as found in yeast, and the peroxide derivative.

The Problem of Newcastle Disease

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Newcastle disease, the predominant form of fowl pest in Britain, can only be effectively controlled if improvements in vaccines and methods of administration are coupled with better farm hygiene.

THE term "fowl pest" refers to two different diseases. The first to be described was fowl plague which is a rare virus infection of chickens caused by a strain of influenza virus first recorded in Italy in 1878. This is a rapidly lethal poultry disease, characterized by high fever, cyanosis and rapid death. The disease shows little tendency to spread, however, and has seldom proved difficult to control. The second disease is Newcastle disease which is now widespread in most countries. As the two diseases are both respiratory diseases of chickens caused by viruses and give rise to symptoms which are not dissimilar, they are for legislative purposes referred to together under the heading of "fowl pest". Nearly all the cases of fowl pest which have been recorded in Britain have been caused by Newcastle disease virus with only two recorded cases of fowl plague since 1929. The 1970 epidemic was caused by a strain of Newcastle disease virus which is both more virulent and more contagious than previous isolates, and it is this virus which causes constant losses in the chicken populations in most countries; it is the one which can cause severe economic losses unless effective control measures are constantly practised.

Early Evidence

The infection causes respiratory symptoms in its milder form and in the case of the more virulent strains these are more severe and are accompanied by severe nervous involvement leading to paralysis and death. The disease was described by T. M. Doyle, a research worker in this laboratory, who investigated a series of outbreaks of a hitherto unrecognized disease among chickens in the Newcastle upon Tyne area in 1926. In the same year the disease was described by Kranveld in Batavia and after this it was reported from various countries, chiefly around the Indian Ocean and nearly always close to seaports. This suggests that the disease was spread by man. Its origin is, however, still obscure. Crawford first diagnosed the disease in Ceylon and suggested that its spread may have been associated with the transport of chilled meats that was developing in the 1920s and the discharge of the offal of poultry and of game birds which were carried in ships' stores.

One of the few initial cases that was recorded was at Rhaniket in India which is about 600 miles from the sea; after the appearance of the disease there it spread steadily across India. The effects of the disease were sufficiently dramatic for us to be sure that it had not been seen in that country before 1927, and although little is recorded of diseases of poultry in Asia before the 1920s there is nothing to suggest that it had been seen in domestic poultry before 1926. An attractive theory is that the virus had existed and still exists commensally in some species of wild birds from

which it occasionally escapes into domestic poultry, causing recognizable disease. Circumstantial evidence suggests that this commensal state exists in species which inhabit South-East Asia, but it is almost certain that the reservoir does not exist in more temperate climates. The virus has been recovered from a large number of species in many parts of the world. Cases in Europe, however, almost certainly arise from cross contamination from outbreaks of disease in domestic fowls and, with the exception of pheasants, disease in non-domesticated birds seems to be very limited.

Until about 1940 outbreaks of the disease tended to be rather sporadic although in individual flocks the condition was severe. At this time the disease had not been recognized in America and it was not until 1944 that Beach showed that the relatively mild condition which had existed for several years in the United States under the name of avian pneumo-encephalitis was in fact a mild form of Newcastle disease.

The milder forms of the disease were usually found in temperate climates, whereas the more virulent forms occurred in the tropics; outbreaks of intermediate virulence were evident around the Mediterranean. From time to time the more virulent forms of the disease have spread but they have tended to subside after control by vaccination and isolation or slaughter, leaving a lower level of less virulent disease. The most dangerous form of the disease is caused (as in the present outbreak) by a virus which is not of extreme virulence but which spreads too rapidly for control by slaughter because of its high contagion. It causes a heavy buildup of virus which provides a severe challenge to birds with no or little immunity. Under favourable conditions the spread of such a virus from one set of premises to another can be very rapid.

During and after the Second World War the disease continued to spread from country to country and the total incidence rose steadily. In the early stages when poultry flocks were fairly small and more self-contained, many of these cases were self-limiting. As the poultry industry grew in size and intensity, however, the spread of the disease became more rapid until in areas of intensive poultry keeping it became endemic.

By this time vaccines to control the disease had been developed. The first was produced from a virulent form of the virus isolated in Hertfordshire in 1933 and was developed by Iyer, a visiting Indian worker who—in conjunction with Dobson—successfully attenuated the virus by repeated passage in fertile hen eggs. On his return to India, Iyer and his colleague Idani set about repeating the work with a local Indian strain and produced the very successful if somewhat virulent vaccine called the Mukteswar strain, which is now used all over South-East Asia. This strain was also used by Simmins during the war in Palestine, and, although effective, was considered to have too much residual pathogenicity. This stimulated the development of another strain which is slightly safer and has been named after the originator as the Haifa-Komarov strain. Vaccine from this strain is now used widely throughout Africa and the Middle East and in Russia.

These strains all possess considerable residual virulence and are not suitable for areas where the effects of the disease are more mild and where competition rules out the use of agents which might cause reactions severe enough to affect production. In the United States, where less pathogenic

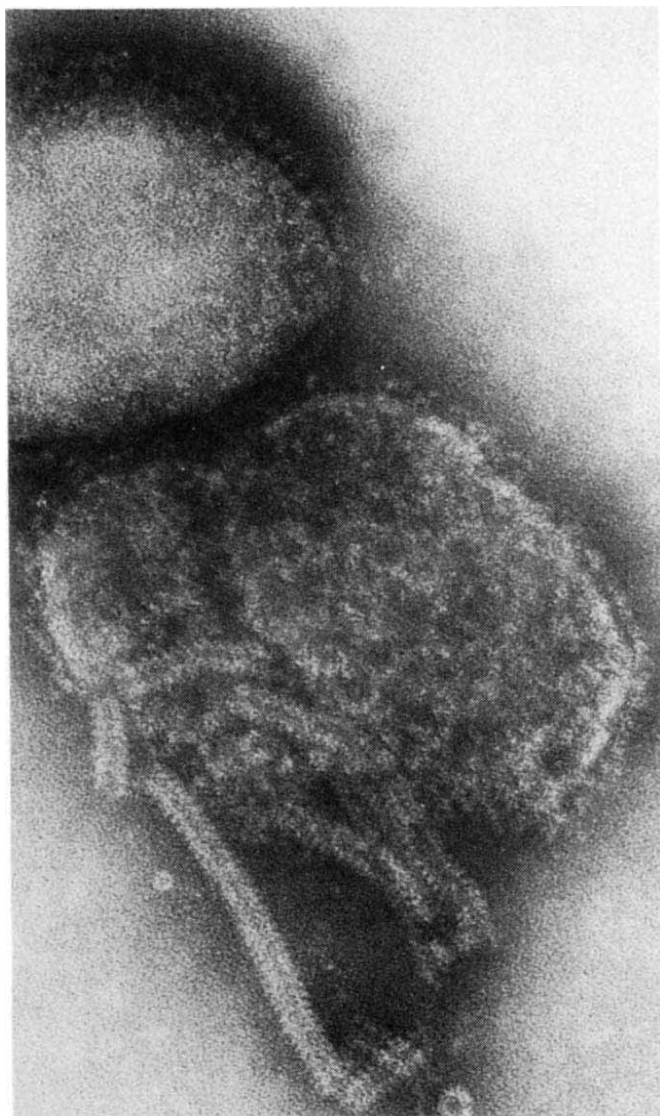


Fig. 1 Two Newcastle disease virus particles. The upper one is intact whereas the lower one is broken and the helical internal component is visible. This internal component is the ribonucleoprotein of the virus and the membrane is the virally altered cell membrane component. ($\times 250,000$.) This micrograph was kindly supplied by Dr June D. Almeida, Royal Postgraduate Medical School, DuCane Road, London W12.

strains existed naturally, Hitchner selected one which was naturally avirulent and tested it as a possible vaccine. This strain—the B1—has become the most widely used vaccinal strain in the world and has been followed by several others all characterized by their intrinsically low virulence combined with a residual ability to invade the chicken's respiratory tract,

By 1950 the disease had become the largest potential cause of loss to the chicken farmer, and a variety of control measures had come into force. Where the incidence of a virulent virus made disease recognition straightforward and where the incidence of the disease was low, control by slaughter was adopted. In Asia control was by vaccination, usually with a mild virus of the B1 type at first and then by the individual application of the Mukteswar strain. In the United States, the somewhat lower virulence of the naturally occurring field virus allowed less rigorous control measures to be adopted and the mass application of the B1 and related LaSota strains has been the most widely adopted method of control.

But these mild or attenuated live virus vaccines can still induce a small amount of respiratory disease which can in

some instances be complicated by secondary infections, so their use does not constitute an ideal form of control. When Britain ceased to use compulsory slaughter of infected flocks it was decided to use an inactivated vaccine which had recently been developed to a high standard. Its use brought the 1962 outbreak under control by stages, although the incidence of disease did not fall rapidly until vaccination was coupled with an increased standard of hygiene. When this was achieved the incidence of disease decreased year by year until in the summer of 1969 only one case a month was reported.

Vaccine controls the disease by reducing the death rate, and also by drastically reducing the number of infected particles shed. Poultry rearing is a very competitive industry and, inevitably, the use of vaccine became less extensive as the incidence of the disease was reduced. The number of completely susceptible birds then increased, and it was clear that a disease vacuum was being created; members both of the poultry industry and of the veterinary profession urged that a high level of vaccination should continue.

By the middle of 1970, less than half the national flock was receiving vaccine and when the disease erupted in Essex the initial spread was very rapid, partly because of the infection of a large number of susceptible birds in an area where the poultry industry is particularly dense, and partly because of the large quantities of virulent virus released by each of them.

In the present epidemic, the losses are not only due to the inherent virulence of the virus, but also to the unusually high buildup of infective virus which occurs because this strain is unusually active in the respiratory tract, and is released from infected birds in much larger amounts than strains which have a more fixed neurotropic activity.

It is not uncommon to consider disease control simply in terms of the application of sufficient vaccine to immunize the population. In the case of Newcastle disease—as with other infectious conditions—several factors complicate the issue. These include the buildup of virus in large poultry houses, thus placing neighbouring flocks in jeopardy because of the possibility of spread of the virus by wind and the likelihood of mechanical transfer from one site to another. If poultry houses are saturated, the virus buildup also increases the chance of virus carrying over from one crop to another unless disinfection between batches is meticulously carried out.

Of equal importance is the problem of unusually high levels of antibody in the breeding flocks which develop as a result of disease. These are transferred passively to the young chick through the yolk sac, and can neutralize the effect of vaccination for a variable length of time. This means that some birds can be successfully immunized soon after hatching but others are refractory until they are more than 6 weeks old. When chicks such as these are placed in contaminated surroundings, they cannot be protected by immediate vaccination, and are liable to develop the disease as soon as their maternally derived protection wears off.

Mass Vaccination

In an effort to minimize the losses that can occur in this way it is now common practice to immunize large groups of broiler chickens several times early in life in an attempt to obtain a satisfactory immune response in as many as possible at the earliest possible age. Application of vaccine to 100,000 or more birds on one site makes individual handling almost impossible, and mass vaccination methods (mixing the vaccinal virus in the drinking water or applying a fine spray of virus into the chicken house) are usually employed. The technique adopted in the last of these methods is fairly critical as too small a droplet size will cause deep penetration of virus into the lungs or air sacs where it can set up a severe reaction. In smaller flocks, such as breeder replacements,

the most satisfactory way of achieving a useful and even immune response is by individual administration of a drop of vaccine into the conjunctival sac from which it travels by way of the naso-lachrymal duct to the upper respiratory tract, thus multiplying and inducing the immune response.

In the case of influenza vaccines, the choice of the correct antigenic type of vaccinal virus is all-important. Newcastle disease virus, on the other hand, belongs to the paramyxovirus group which includes the viruses of mumps, measles, rinderpest and distemper; these viruses are each antigenically homologous and therefore the problem of plurality of antigenic types does not arise. The apparent failure of vaccines for Newcastle disease has led many workers to suggest that some antigenic variation might exist and until recently the problem had not been satisfactorily solved. In an attempt to settle the question a number of research workers have worked jointly on a programme of analysis of a variety of strains of virus drawn from different parts of the world. Pennington carried out a series of cross-neutralization tests which showed that although homologous virus serum mixtures were neutralized at a faster rate than similar heterologous mixtures, there was no distinct variation between strains which might create the need for vaccines of more than one antigenic type. Similar studies were carried out by myself, Kendal, Reeve and Alexander which included a comparison of the enzyme neuraminidase from fourteen different strains. Although there was considerable variation in the growth kinetics of different strains and their ability to form plaques, there was no measurable serological variation between any of the isolates examined. The efficacy of vaccines therefore probably depends more on their quality and the efficiency with which they are administered than on any antigenic variation. It would indeed be unlikely for any member of this group of viruses to show such variation.

The efficiency of a live virus vaccine depends on its invasiveness and its power to multiply sufficiently within the chicken to set up an adequate immune response. As the invasiveness of a strain is directly related to its level of virulence, the more efficient immunizing strains are also those which will induce the most severe reactions. It was this consideration which led Britain to adopt a policy of vaccination limited to inactivated vaccines which can now be produced with high potency. Such vaccination proved very effective and it was the reluctance of the poultry industry to spend the time and money on techniques of individual inoculation which led to its eventual failure.

The addition of live virus vaccines to the drinking water is simple and cheap but the method is not very effective because the site at which the virus multiplies is the respiratory tract. It is believed that only that virus which splashes onto the nostrils and comes in contact with the respiratory tissues around the pharynx can multiply successfully. Virus which reaches the proventriculus is rapidly destroyed. The optimal dose of virus is between 10^6 and 10^7 infective particles and it is important that as much as possible of this dose reaches the respiratory mucosa of the bird. Although these vaccinal viruses are contagious, their spread is limited and the immune response that takes place is a direct function of the amount of virus introduced.

An effective response is dependent on the presence in the bird of the equivalent of about $10^{9.5}$ infective particles. To achieve this, live virus vaccines which come into contact with the bird in concentrations less than one five-hundredth of this amount must successfully invade the bird and multiply sufficiently to provide an adequate stimulus. When the bird is in the fully susceptible state this potential can be achieved, but when circulating antibody—which may be either actively or passively acquired—is present it may inhibit the multiplication of the vaccine. This makes the timing of repeat doses of vaccine particularly difficult as the chicken must be susceptible to infection before a satisfactory reinfection can take place. When there are large quantities of field virus

the chance of field infection is high. The mild live virus vaccines do not multiply very efficiently when used as boosters of existing immune levels and so the secondary response that they induce is seldom very much higher than the primary response. This may be overcome by using the more invasive live virus vaccines for repeat vaccination or injecting the inactivated vaccine which is combined with a mineral adjuvant and induces a very satisfactory secondary response.

Other recent work has involved studies into the immunosuppressive nature of another poultry virus infection. My colleague, J. T. Faragher, has shown that infection early in life with the infectious bursal agent, which is thought to be a reovirus, can cause a significant depression of antibody levels to subsequent Newcastle disease vaccines. Continuing work will be designed to assess the importance of this infection as a complicating feature of Newcastle disease control.

Improving Control

Improvements in vaccines, their administration and farm hygiene are essential if more effective control over the disease is to be achieved. The live contagious vaccines of the B1 type produced in egg embryos are unlikely to be further developed although increasingly more stringent government requirements for their safety and potency now ensure that all vaccines which are available are close to their optimal level. Live vaccines produced in tissue culture systems have been available in other countries for several years. They are considered to be effective, but as they require to be injected they are more than usually susceptible to neutralization by existing immune levels. Inactivated vaccines depend for their potency on the amount of viral protein that they contain, and although tissue culture methods of production simplify the production processes it is doubtful whether they can match the virus yields obtainable in embryonated eggs. Slow growing strains multiply to a higher level than those which cause rapid death of embryos and by using these it is now possible to produce inactivated vaccines of considerable potency. Their cost and the cost of injecting birds individually means that their use will probably be confined to breeder and replacement flocks.

Programmes of administration pose additional problems. In an effort to find a compromise between the easy but relatively inefficient method of applying vaccine in the drinking water and the effective but laborious method of individual application by the ocular route, there is increasing interest in the application of the virus by spray; this is in spite of the serious side effects which can occur if the conditions of application are wrong or if the flock is predisposed to respiratory disease.

Vaccination alone cannot provide the answer. The emergence of Newcastle disease as a world problem has been closely linked to the gradual intensification of the poultry industry, and an effective programme of vaccination must be coupled with standards of hygiene that help to limit the spread of virus and, in particular, to eliminate the infection from a site following disease. The difficulty of doing this increases with the size of the units concerned, and it is known that the amount of infective virus that can be shed as windborne infection from a severely infected and sizable unit can be as much as $10^{9.0}$ infective particles per hour. Although windborne infection can play a large part in the spread of disease from severe outbreaks, the persistence of disease in an area is related to a greater extent to group practices involving rapid restocking after an outbreak of disease and the failure to segregate one production unit from another. The problems of intensification will become greater as the production of poultry increases and, to prevent a recurrence of the epidemic, continued vaccination must be coupled with improved hygiene even if this leads to increased costs.

Detection of Plutonium-244 in Nature

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Mass spectrometric measurements of plutonium isolated from Precambrian bastnasite confirm the presence of ^{244}Pu in nature. Although the existence of ^{244}Pu as an extinct radioactivity has been postulated to explain the xenon isotope ratios observed in meteorites, this is the first indication of its present existence in nature.

THE agreement between recent measurements of the Xe isotopic ratios from spontaneous fission of ^{244}Pu by Alexander *et al.*¹ with the corresponding ratios found in achondritic meteorites strongly supports the existence² of ^{244}Pu in the early solar system. But attempts to detect residual ^{244}Pu in nature have previously been unsuccessful, and the most recent investigation reported by Fields *et al.*³ resulted only in an upper limit of 3×10^{-22} g/g for the average terrestrial abundance of ^{244}Pu . This limit is still well above the upper limit for the present average terrestrial abundance of 3×10^{-25} g/g which can be calculated by assuming that 4.7×10^9 yr ago, the abundance of ^{244}Pu (half-life = 8.28×10^7 yr⁴) was equal to the present average terrestrial abundance⁵ (4.4×10^{-8} g/g) of ^{232}Th , the ultimate decay product of ^{244}Pu . Because even the most sensitive mass spectrometric measurements require $\approx 10^7$ atoms ($\approx 4 \times 10^{-15}$ g) of Pu for positive detection, it is necessary to process very large samples of ores which are highly enriched in Pu.

We describe here the isolation of the Pu fraction and the subsequent detection of 2×10^7 atoms (8×10^{-15} g) of ^{244}Pu from about 85 kg of ore containing bastnasite, a rare earth fluorocarbonate mineral. We also discuss the implications of the presence of ^{244}Pu in nature in the establishment of the last time of formation of the heavy elements prior to the formation of the solar system, and consider the possibility that ^{244}Pu may occur as a result of accretion from a steady state cosmic ray source.

Source of Bastnasite

Our starting material consisted of about 9 l. of 25% di-2-ethylhexylorthophosphoric acid (HDEHP) in kerosene, and was provided by the Molybdenum Corporation of America from an inventory of extractant used to purify Ce derived from a bastnasite deposit mined at Mountain Pass, California. Our

sample represented the processing of about 10.5 kg of pure CeO_2 which is equivalent to 26 kg of bastnasite, or 260 kg of "as-mined" ore. This ore typically contains about 10% bastnasite together with 50% calcite, 25% barite, and 15% silica, strontianite, chlorite, monazite, galena and so on. Hot-froth flotation, acid leaching, and calcining are used to prepare a rare earth concentrate which is then roasted to convert any Ce(III) to Ce(IV). It seems probable that any Pu in the bastnasite would be concentrated in the rare earth fraction and would be present as Pu(IV), regardless of its initial oxidation state, because Pu(III) is more readily oxidized than Ce(III). After removal of the trivalent rare earths by dissolution in dilute HCl, the CeO_2 is dissolved and finally purified by extraction into HDEHP and back extraction with dilute HCl containing H_2O_2 . Because Pu will extract into HDEHP but will not back extract under these conditions⁶, any Pu present in the bastnasite should accumulate in the HDEHP as it is recycled.

Isolation of Plutonium

The HDEHP sample was divided into three approximately equal fractions which were processed separately. ^{236}Pu and ^{242}Pu were used to determine the amount of ^{244}Pu in each fraction. Known amounts were extracted into the HDEHP from 3 N HCl containing NaNO_2 to ensure that the Pu was present in the (IV) state. The aqueous phase from this extraction was checked to make certain that at least 99% of the tracers had extracted. The HDEHP was then washed with 10 to 15 l. of 6 N and 3 N HCl in 500 ml. portions to remove macroscopic impurities such as Fe or Ce. When no more mass could be detected in the washes by hydroxide precipitation, the Pu was back extracted by an adaptation of our procedure for separating Pu from large volumes of solution⁶. One litre of 2,5-di-tertiary butylhydroquinone was added directly to the HDEHP to reduce Pu to the (III) state and complex it. It was then back extracted twice by treatment with 2 l. of 6 N HCl. The combined back extractants were washed with kerosene and then evaporated to dryness under vacuum. Although very little Th should back extract in these conditions, the mass spectrometric analysis of fraction I indicated interference from Th. In subsequent analyses, the Pu was adsorbed on 7 mm internal diameter $\times$ 10.5 cm long anion resin columns and eluted with an HI-HCl mixture according to a standard Pu procedure (page 91, ref. 6). No interference from Th was encountered after this step was added. The Pu fraction eluted from this column was further processed just prior to isotopic analysis by extraction into 0.2 M thenoyltrifluoroacetone and back extraction with 8 N HNO_3 . We have found this necessary

to reduce solids and other interferences which lower the efficiency of plutonium ion emission in the mass spectrometer.

The ^{236}Pu and ^{242}Pu tracers, complete process blanks, and appropriate volumes of new batches of reagents were analysed for ^{244}Pu . None of these showed ^{244}Pu . Our chemical yield for complete processing of Pu from HDEHP was $>95\%$.

Mass Spectrometric Measurements

The thermal ionization plutonium isotopic measurements were all obtained utilizing rhenium V-type filaments⁷ in the KAPL three stage⁸ mass spectrometer in the pulse counting mode⁹. The first Pu fraction from the bastnasite contained too much Th for analysis. Although Th was eliminated from the second fraction, the sample still did not yield a sufficient number of ions of ^{242}Pu tracer to permit a good analysis, but the upper limit of 5×10^7 atoms of ^{244}Pu found is not inconsistent with the actual amount of ^{244}Pu found in the third fraction.

^{244}Pu was found in the third fraction of the bastnasite ore and was confirmed by mass spectrometry in two separate aliquots of this third fraction. The first aliquot gave a value for $^{242}\text{Pu}/^{244}\text{Pu}$ of 284 ± 40 while the second aliquot gave a value of 266 ± 40 . The $^{244}\text{Pu}/^{242}\text{Pu}$ ratio was observed to be constant over the normal range of filament temperature (specifically, eight temperature increments). This temperature range was consistent with our experience in plutonium ion emission. Table 1 shows the mass spectrometric results obtained from the third fraction of the bastnasite. A total of 268 ions were detected at the ^{244}Pu mass position of which 26 are ascribed to instrument noise.

Table 1 Mass Spectrometric Determination of Isotopic Abundances in Plutonium Fraction III from Bastnasite

Pu mass No.	Atoms ($\times 10^{-7}$)
236	280
238	<10
239	280
240	≈ 18
242	565 (tracer)
243	<0.2
244	2.0

During the course of this work, mass spectrometric analyses of tracers, reagent blanks, and process blanks have been performed. None of these showed ^{244}Pu . Of the tracers used, ^{236}Pu gave the highest upper limit, $<1.7 \times 10^5$ atoms, for ^{244}Pu . Of the six process and reagent blank analyses, two gave upper limits of <4.6 and $<5.5 \times 10^6$ atoms for ^{244}Pu while all the other analyses gave limits of $<1.5 \times 10^6$ atoms. Our experience has shown that chemically pure tracers give an order of magnitude better ion emission than an equivalent amount of Pu which has undergone extensive processing before being introduced into the mass spectrometer. The higher limits observed for the process and reagent blanks than for the tracers reflect this reduction in sensitivity, which is attributed not to low chemical yields but to the influence of some unknown and uncontrolled trace impurity which inhibits plutonium ion emission. This observation is entirely consistent with our experience with the large number of trace Pu analyses conducted during the past 15 yr.

Two process mock-up analyses (without HDEHP) were also made in which 1.75×10^6 and 1.75×10^7 atoms of ^{244}Pu , respectively, were introduced along with the ^{242}Pu tracer. The mass spectrometric analyses indicated 2.02×10^6 and 1.95×10^7 atoms, respectively.

The absolute amount of ^{244}Pu detected in the third fraction of the bastnasite sample was 2.0×10^7 atoms, calculated from the $^{242}\text{Pu}/^{244}\text{Pu}$ measured ratio and the known amount (5.65×10^9 atoms) of ^{242}Pu tracer added. In addition, the measured

amount of ^{236}Pu (Table 1) agreed with the 2.88×10^9 atoms of ^{236}Pu tracer added. The only correction made to the observed data was for instrument noise. Correction for possible ^{244}Pu contributions by the tracers and process blanks was not made since the data available for this were "upper limit" observations. These "upper limits" amounted to between 15% and 20% of the ^{244}Pu actually found in the bastnasite. We elect not to make an empirical correction of this type because of the data resulting from our mock-up samples. For example, in the 1.75×10^6 atoms of ^{244}Pu mock-up, we measured 2.02×10^6 atoms. This excess of 0.3×10^6 is less than 2% of the ^{244}Pu found in fraction III. Similarly, in the mock-up sample containing 1.75×10^7 atoms of ^{244}Pu , we measured 1.95×10^7 atoms. This excess of 0.2×10^7 atoms does amount to approximately 10% of the ^{244}Pu found, but could as well be caused by the imprecision of the measurement at this level. Imprecision of measurement is, of course, included in our results for the third fraction of the bastnasite.

In summary, 2.0×10^7 atoms of ^{244}Pu were found in the sample. In assigning an error to this value we include $\pm 10\%$ for precision of the measurement, $\pm 5\%$ for uncertainty in the background correction, and a possible 20% positive bias when one considers the upper limits derived from the blank runs. Thus the best estimate becomes $2.0^{+0.3}_{-0.7} \times 10^7$ atoms of ^{244}Pu per 8.5 kg of bastnasite, or 1.0×10^{-18} g ^{244}Pu /g.

The $^{239}\text{Pu}/^{244}\text{Pu}$ ratio was found to be 140 for fraction III. This low value rules out any possibility of the ^{244}Pu being due to atmospheric fallout from world-wide debris, from Nevada underground heavy element producing devices, or from highly burned reactor fuel. There is, of course, the highly remote possibility that a submicron particle of pure ^{244}Pu could somehow have been incorporated into our sample. However, ^{244}Pu had never been handled previously in the new laboratory at LASL where the processing was done, and clean room techniques were used during the course of the work.

Implications of ^{244}Pu in Nature

The bastnasite from which our sample was derived is reported to be a Precambrian deposit. The CeO_2 in the pure bastnasite is typically 30% to 50%, indicating an enrichment of the order of 5×10^5 over its average terrestrial abundance¹⁰ of 9×10^{-7} g/g, or about 10^4 over its abundance in the Earth's crust. If one takes Podosek's¹¹ value of 0.013 for the ratio of ^{244}Pu to ^{238}U at the time of meteorite formation 4.56×10^9 yr ago, the present abundance of ^{244}Pu is 7×10^{-27} g/g based on an average terrestrial value⁵ of 1.1×10^{-8} g/g for ^{238}U . Our single result for bastnasite indicates 10^{-18} g/g which would require an enrichment of about 1.4×10^8 for ^{244}Pu , or about 2.8×10^2 relative to Ce. On the other hand, if the ratio of ^{244}Pu to ^{238}U is as high as 0.5, a possibility indicated by Fleischer *et al.*¹², the present abundance of ^{244}Pu is 2.8×10^{-25} g/g which requires an overall enrichment for ^{244}Pu of 3.0×10^6 or only about 6 relative to Ce. The bastnasite is believed to vary widely in both Th and U content so variations in ^{244}Pu content may be expected. If, however, the detection of ^{244}Pu is substantiated at something like 10^{-18} g/g in other samples of bastnasite, it would tend to support the hypothesis that *r*-process nucleosynthesis was occurring at the time of formation of our solar system, since unreasonably large enrichment factors (for example, $>10^{12}$ for 6×10^9 yr) would be required if the last synthesis occurred much longer than 5×10^9 yr ago.

The possibility of ^{244}Pu resulting from a steady state cosmic ray source must also be considered. Dr George Bell of the Los Alamos Scientific Laboratory has pointed out to us that the present abundance of ^{244}Pu due to the influx of ^{244}Pu nuclei in cosmic rays may be comparable with, or greater than, that surviving from primordial Earth material. If the steady state, upper limit incident flux of ^{244}Pu nuclei is assumed¹² to be 10^{-11} cm^{-2} s^{-1} , if the probability that an incident nucleus is stopped without undergoing disintegration is 0.1, and if, in a length of time of the order of a ^{244}Pu half-life as much as 10 km

of the Earth's crust may be involved in the distribution of ^{244}Pu , the concentration of ^{244}Pu would be

$$\frac{(10^{-11} \text{ } ^{244}\text{Pu atoms cm}^{-2} \text{ s}^{-1})(0.1)(4 \times 10^{15} \text{ s})}{(2.5 \times 10^{21} \text{ atoms } ^{244}\text{Pu/g})(3 \times 10^6 \text{ g cm}^{-2})} = \approx 5 \times 10^{-25} \text{ g/g}$$

This value is comparable with the upper limit for ^{244}Pu derived from ^{232}Th , and higher than the values calculated from the ^{244}Pu to ^{238}U ratios obtained from meteorites. If this bastnaesite is $>5.5 \times 10^8$ yr old, the plutonium must have been incorporated in the mineral that long ago with no further enrichment possible. The decay factor for ^{244}Pu during this time would be about 100, reducing the concentration to about 5×10^{-27} g/g, thus requiring an enrichment factor of about 2×10^8 to give the 10^{-18} g/g reported here.

It is obviously important to confirm the present single result on larger samples of the same ore. Extension of the measurement to minerals whose age is much less than the half-life of ^{244}Pu might help in deciding whether the ^{244}Pu is primordial or originates from a cosmic ray flux. In the latter case, concentrations of ^{244}Pu up to 100 times as large might be expected since very little decay would have occurred since enrichment, that is, formation of the mineral. In fact, if reliable measurements of different age samples of a given mineral could be made, it might be possible to infer something about the magnitude of the cosmic ray flux. Measurements of other minerals, such as gadolinite, in which U, Th, and the rare earths have nearly the same enrichment factors would also be valuable since the enrichment factor for Pu might be expected to be similar. Then, if a much higher enrichment for Pu were observed, a cosmic ray origin might be indicated.

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Simplicity of Mammalian Regulatory Systems inferred by Single Gene Determination of Sex Phenotypes

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Dr Ohno predicts that mammalian regulatory systems will turn out to be less complex than is generally anticipated.

It has often been stated that compared with the *lac* operon system of *E. coli*¹ and other regulatory systems of prokaryotes, genetic regulatory systems in mammals must be enormously complicated, defying meaningful analysis at present. I suggest that this is as unsound as the notion that, since the mammalian genome contains 750 times more DNA than that of *E. coli*, the genome of which seems to contain about 4×10^3 genes, mammalian genomes must specify 3×10^6 different gene products.

All gene loci are affected by mutations, and mutation in a gene often contributing to the wellbeing of an organism would

be detrimental. For example, mutational deficiency of individual lysosomal enzymes causes eleven different lysosomal diseases in man, many of them extremely severe². As the spontaneous deleterious mutation rate per locus per organism generation is of the order of 10^{-5} , an organism with 3×10^6 genes would be exterminated by the excessive mutation load (the overall deleterious mutation rate per generation becomes thirty). Kimura³ estimated that if all the mammalian genomic DNA are functional genes, in order to maintain a stable population size, each mated pair would have to produce 10^{78} zygotes to assure that a few of them would survive. Because of what Haldane⁴ termed "the cost of natural selection", Muller⁵ as well as Crow and Kimura⁶ concluded that the human genome must contain only 4×10^4 or so genes. This number of genes accounts for only a fraction of the total DNA in the human genome. The concept that most of our genomic DNA is noninformational seems to be accepted by an increasing number of investigators⁷.

When one realizes that the mutation load imposes a finite upper limit to the number of gene loci which an organism can afford to have, it becomes clear that, during evolution from unicellular prokaryotes to multicellular eukaryotes of increasing complexity, the necessary increase in number of regulatory systems had to be compensated by simplifying each regulatory system. I contend, therefore, that the direction of natural selection has been to reduce the number of components in each regulatory system as multicellular organisms attained higher degrees of complexity.

In mammals, the dosage compensation for most, if not all, *X*-linked genes is accomplished in one step by inactivation of one or the other *X* in the female⁸. It would not be surprising if a single gene locus controls this inactivation process involving hundreds of structural genes. The beauty of this mechanism is in its simplicity.

phenotypes in mammals. The minimal requirement for sex determination is a set of two regulatory genes: one to mediate the developmental direction of indifferent gonads toward either testes or ovaries and the other to regulate the manifestation of secondary sex characteristics. I am concerned here only with the second regulatory system, and, for this system, the testis or the ovary merely serves as the supplier of an inducer (steroid hormone).

Sex Phenotypes

In a series of embryological experiments on rabbits and rats, Alfred Jost¹⁰ has shown that the expression of the male or female phenotype strictly depends on the presence or absence of testosterone (an inducer) (Fig. 1). If *XY* embryos are castrated early enough, the Müllerian ducts automatically differentiate to Fallopian tubule and uterus, while the Wolffian

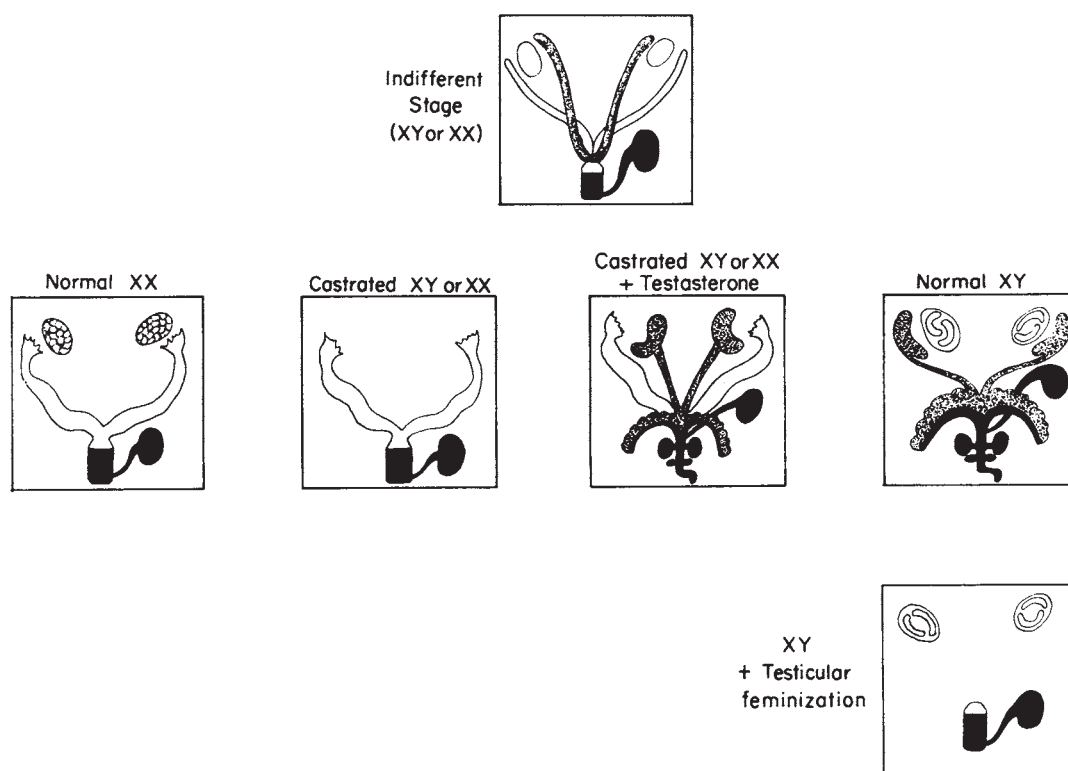


Fig. 1 A scheme (modelled after Neumann *et al.*³²) showing the role of testosterone and the effect of the *Tfm* mutation on the embryonic development of the Wolffian duct (shaded), Müllerian duct (outlined) and urogenital sinus (solid black). The pair of bean-shaped bodies at the top of each square signify gonads: indifferent gonad (outlined), ovary (filled with small circles) and testes (containing two tubules).

In the inducible regulatory system of mammals, hormones rather than substrates, or derivatives of substrates, serve as inducers. Accordingly, in addition to the components of regulatory systems in target cells, the genes concerned with synthesis and release of hormones in endocrine cells contribute to the mutation load. The observation that the actions of a multitude of peptide hormones are mediated through a small variety of intracellular inducers such as cyclic AMP⁹ supports the view that natural selection favoured economy and simplicity in mammalian regulatory systems.

Selective pressure for simplicity must have been especially strong for the genetic regulatory system concerned with sexual development, for a mutation which results in sterility is lethal: those which do not reproduce are genetically dead. I will develop the thesis that a single gene product specified by the *X*-linked locus controls the expression of male and female

ducts retrogress. Accordingly, an embryo acquires the female phenotype. The administration of testosterone to castrated *XY* or *XX* embryos sustains the development of Wolffian ducts toward ductus deferens, epididymis and seminal vesicles and directs the differentiation of the urogenital sinus toward prostates and penis formation. Externally administered testosterone, however, fails to destroy Müllerian ducts and these castrated embryos have the hermaphroditic phenotype. On this basis, Jost reasoned that the destruction of Müllerian ducts requires the presence of another male hormone (factor "X") secreted by embryonic testes.

Jost's experiments completed the demonstration that maleness and femaleness can represent an induced state and a non-induced state of one and the same regulatory system. The regulatory gene product of this system must have a binding affinity to testosterone or its metabolites, or both.

Testicular Feminization

If this regulatory gene product loses binding affinity by mutation, testosterone would become totally ineffective. Such a mutation would not affect the development of *XX* females, but the *XY* male should show externally a female phenotype in spite of the presence of testes. Factor "X" secreted by testes would destroy the Müllerian duct and the Wolffian ducts not responding to testosterone would also disappear. The urogenital sinus remaining unmodified would form the vagina which ends as a blind sac (Fig. 1). This phenotype is, of course, that of the well known inherited testicular feminization syndrome originally described in man^{11,12}, and subsequently found in cattle¹³, rats¹⁴ and mice¹⁵.

clearly established that this mutation resides on the *X* chromosome. Lyon and Hawkes¹⁵ were able to show the very close linkage between this *Tfm* locus and two well known *X*-linked coat marker genes of the mouse; tabby (*Ta*) and blotchy (*Blo*). As a gene which is *X*-linked in one mammalian species is almost always *X*-linked in other species¹⁸, we infer that the *Tfm* locus resides on the *X* chromosome of all mammalian species.

In mice, *Tfm* behaves as a point mutation and, in man, Jagiello and Atwell¹⁹ estimated the spontaneous mutation rate of *Tfm* to be $0.4-0.5 \times 10^{-5}$ per generation; also compatible with the view that the mammalian genome contains only one gene locus which can mutate to give this particular phenotype.

The nature of control exercised by this single locus in target

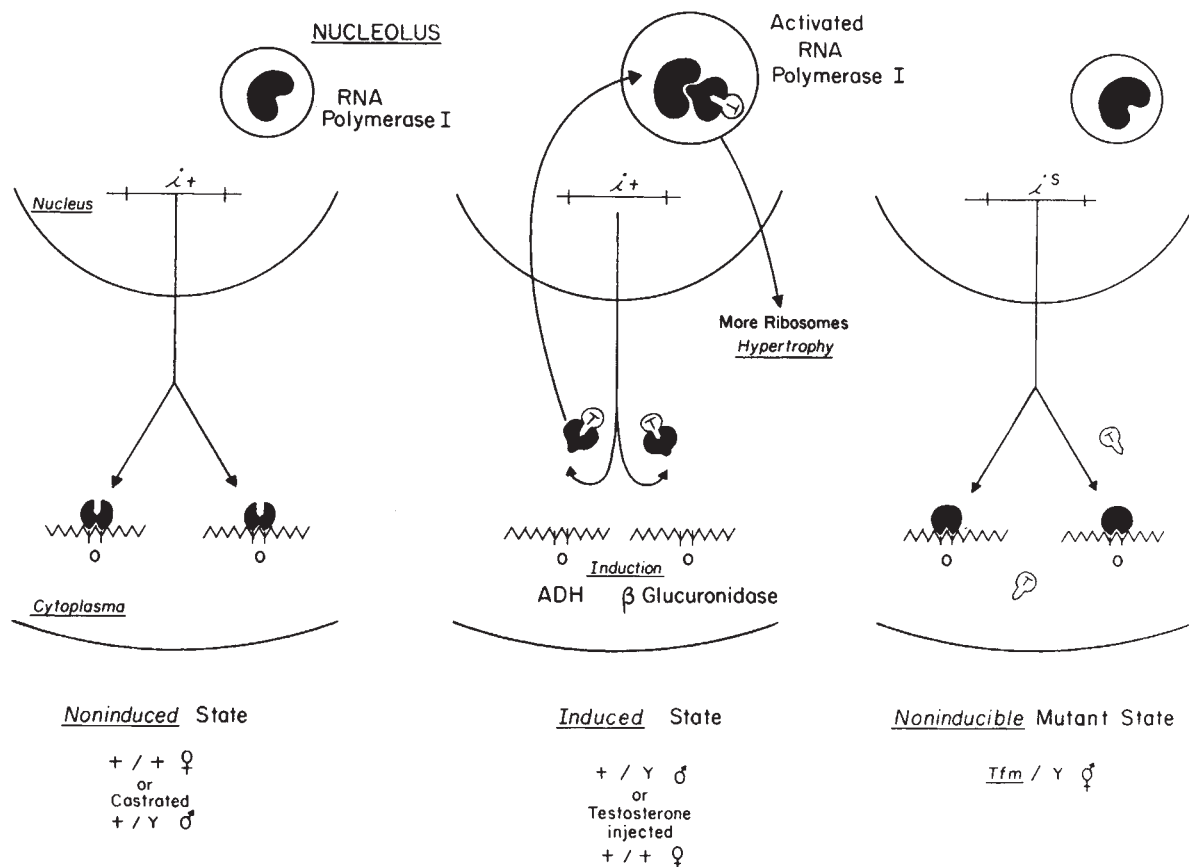


Fig. 2 A scheme illustrating single gene control of mammalian sexual phenotypes. i^+ represents the wild type allele of the *X*-linked *Tfm* locus. Its product (●) serves as a translational repressor of alcohol dehydrogenase (ADH) and β -glucuronidase in the cytoplasm until the arrival of testosterone (♂). When it becomes bound to testosterone or its metabolites (such as DHT), it moves into the nucleus and activates RNA polymerase I in the nucleolar region, thus causing increased production of ribosomes and hypertrophy. i^s represents a mutant *Tfm* allele; its product (●) has lost the binding affinity to testosterone. The *o* (operator) region in each RNA (wavy line) signifies a homologous base sequence shared by ADH and β -glucuronidase mRNAs which is recognized by the product of *i* gene.

One point must now be clarified. Although testicular testosterone synthesis by affected males of man¹⁶, rats¹⁷, and mice is abnormal due to relative deficiency of either 3 β -hydroxysteroid dehydrogenase¹⁶ or 17 β -hydroxysteroid dehydrogenase¹⁷, the paucity of an inducer (testosterone) cannot be the cause of the testicular feminization syndrome. Affected *XY* surely produce more testosterone than normal females, yet normal females respond to administered testosterone exactly as do normal males, while affected *XY* do not respond at all. The testis is one of the principal target organs of testosterone; thus, testicular insufficiency is merely a consequence of this mutation.

In man, cattle and rats, the mode of inheritance has been compatible with either *X*-linked mutation or autosomal dominant mutation. Only in the case of mice has it been

cells can be ascertained by comparing affected *Tfm*/ $Y \text{♀}$ with $+ / Y \text{♂}$ and $+ / + \text{♀}$.

Tfm Mutation

Target organs of testosterone usually studied are seminal vesicles and prostates, but these organs are not present in $+ / + \text{♀}$ and are missing in *Tfm*/ $Y \text{♀}$. Accordingly, differences in the response to testosterone between $+ / Y \text{♂}$ and $+ / + \text{♀}$, on the one hand, and *Tfm*/ $Y \text{♀}$, on the other, are studied on preputial glands in the case of rats²⁰ and on proximal tubule cells of the kidney in the case of mice²¹⁻²⁴. Proximal tubule cells of the postnatal kidney are closely related ontogenically to Wolffian duct cells as both originate from the nephric blastema.

A single injection of as little as 1 mg of testosterone or 5 α -dihydrotestosterone into +/+ $\varnothing$ or castrated +/Y δ causes a 100 times induction of kidney alcohol dehydrogenase (E.C. 1.1.1.1) and β -glucuronidase (E.C. 3.2.1.31). Testosterone seems to remove the translational block from pre-existing mRNAs, as 5 α -androstane-3 α -17 β -diol which is found only in the cytoplasm can effectively substitute for testosterone as an inducer^{22,23}. Steroid hormone induction of specific enzymes in general seems to involve the removal of a translational rather than transcriptional block²⁵. In *Tfm/Y* kidney, no induction whatsoever of these two enzymes occurs even after the administration of 20 mg of testosterone or 5 α -dihydrotestosterone²¹⁻²³.

Most target organs hypertrophy in response to steroid hormones. Mouse kidney proximal tubule cells are no exception. The administration of 1 mg of testosterone or 5 α -dihydrotestosterone causes 40 to 50% increase in the total kidney weight. Hypertrophy is apparently caused by the increased production of ribosomes on which translation of all the mRNAs depends. Testosterone concentrates in nucleoli of target cell nuclei²⁶ and stimulates a class of RNA polymerase which functions at a low ionic strength²⁷. This is the RNA polymerase which is later identified as a specific RNA polymerase for transcription of rRNA genes in the nucleolar organizing region of the chromosome (nuclear RNA polymerase I of Roeder and Rutter²⁸), it is likely that testosterone causes hypertrophy of target cells by either directly or indirectly stimulating RNA polymerase I. The stimulation by oestrogen of RNA polymerase I has been shown in rat uterus²⁹.

Tfm/Y $\varnothing$ kidney remains atrophic even after the administration of 20 mg of testosterone or 5 α -dihydrotestosterone^{22,23}.

Sixty minutes after an intravenous injection of 45 μ Ci of ³H-testosterone, the *Tfm/Y* cytosol fraction contained 2,000 c.p.m./mg protein of testosterone, 100 c.p.m. of 5 α -dihydrotestosterone and 400 c.p.m. of androstandiols. As the activities of the cytosol fraction of +/+ $\varnothing$ and +/Y δ were no different, it was concluded that the *Tfm* mutation affected neither the uptake by the kidney cytoplasm of testosterone nor intracellular conversion of testosterone.

Amounts of testosterone-binding proteins in the kidney cytoplasm were assayed using ³H-5 α -dihydrotestosterone (DHT) in various concentrations. At a DHT concentration of 1.3×10^{-8} M, proteins in the cytosol fraction of +/+ $\varnothing$ and +/Y δ bound 30×10^{-15} mol/mg protein of DHT after 60 min of incubation at 0 $^{\circ}$ C, while the value for *Tfm/Y* $\varnothing$ was only one-tenth of that for +/+ $\varnothing$ and +/Y δ . It seemed that one class of testosterone-binding protein was entirely missing from the *Tfm/Y* cytoplasm²⁴. As testosterone uptake by *Tfm/Y* cytoplasm was normal, the missing protein was clearly not a specific permease for testosterone.

The *in vivo* uptake of testosterone by kidney cell nuclei of *Tfm/Y* $\varnothing$ was grossly abnormal. No appreciable activity was detected 60 min after the intravenous injection of 45 μ Ci of ³H-testosterone, while kidney cell nuclei of +/+ $\varnothing$ and +/Y δ contained 500 c.p.m./10⁷ nuclei of testosterone. The relative deficiency of nuclear testosterone-binding protein was also noted. At a ³H-DHT concentration of 3×10^{-8} M, proteins in *Tfm/Y* kidney cell nuclei bound 24×10^{-15} mol/mg DNA of DHT after an incubation of 2 h at 30 $^{\circ}$ C, while a three times greater binding was observed in the kidney cell nuclei of +/+ $\varnothing$ and +/Y δ ²⁴.

RNA Polymerase I

On the basis of these findings, I propose that inside the target cells of testosterone a protein specified by the wild type allele of the X-linked *Tfm* locus has a dual role. When it is not bound to testosterone, it stays in the cytoplasm and serves as a repressor of the translation of certain enzymes. Binding with testosterone or its metabolites changes its allosteric configuration, so that the bound form detaches from these mRNAs, releasing a translational block, and moves into the nucleus where it activates RNA polymerase I inside the nucleolar

region (Fig. 2). In this way, a single gene product mediates the entire testosterone-induced response of target cells. Therefore, the loss of this binding affinity to testosterone by mutation simultaneously abolishes responses from all the target organs of testosterone. While testosterone causes hypertrophy in most target organs (activation of RNA polymerase I), different sets of enzymes are induced by testosterone in different target organs of the same species as well as in homologous target organs of different species. In the mouse kidney proximal tubule cell cytoplasm, the *Tfm* protein must be recognizing a short stretch of base sequence homologous in mRNAs of alcohol dehydrogenase and β -glucuronidase. In other target cell cytoplasm, mRNAs for these two enzymes may be absent. Instead, the *Tfm* protein may recognize a similar base sequence on mRNAs of other enzymes.

Proteins in the target cell cytoplasm which have a binding affinity to a steroid hormone have customarily been called cytosol receptor proteins, and it seems that the cytosol receptor protein moves into the nucleus and becomes a nuclear receptor protein^{30,31}. In the case of target cells of testosterone, I propose that the so called cytosol as well as nuclear receptor proteins include a protein specified by the wild type allele of the X-linked *Tfm* locus as the most important component.

According to my scheme, the mammalian genetic regulatory system which governs the expression of sexual phenotypes is as simple as or even simpler than the *lac* operon system of *E. coli*. I believe that most other inducible regulatory systems of mammals are equally simple.

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LETTERS TO NATURE

PHYSICAL SCIENCES

Radio Spectrum of Cygnus X-1

RECENT observations at 2,795 MHz with the NRAO interferometer¹ and at 1,415 MHz with the Westerbork array² have shown that a point radio source appeared in the field of the X-ray source Cyg X-1 some time between March 22 and April 28, 1971. On the basis of strong variability and close proximity, this radio source is identified with Cyg X-1 (refs. 1, 2). Observations with the NRAO interferometer at 2,695 MHz have shown that the source appeared constant in flux from May 13 to July 10, 1971.

We wish to report further observations of Cyg X-1 at 2,695 and 8,085 MHz with the NRAO interferometer and observations at 10,630 MHz with the 150 foot antenna at Algonquin Park, using a beam-switching technique. The results of these observations, together with the results of Braes and Miley, are shown in Fig. 1.

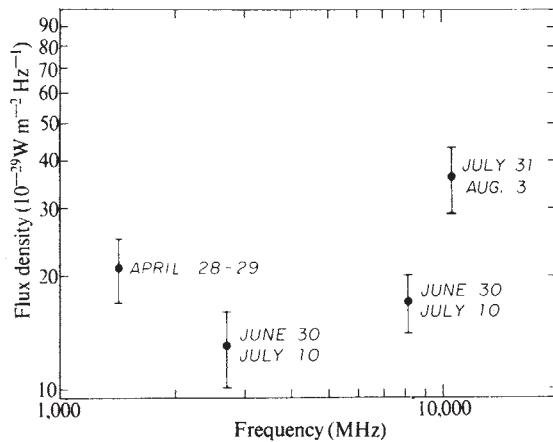


Fig. 1 The radio flux density of Cyg X-1 as a function of frequency. Dates of observation are shown for each data point.

Even though constancy in the radio flux at 2,695 MHz is well established, constancy is not yet established at 8,085 and 10,630 MHz. If, however, no variation has occurred at any frequency between April 28 and August 10, Fig. 1 shows that Cyg X-1 has a peculiar spectrum. Spectra like this are common in quasi-stellar sources (4C39.25, 3C279)³ and some peculiar radio galaxies (3C84)³, although the rise at the higher frequencies is rather steeper. Further spectral observations at many frequencies, but at the same time, are clearly needed so that the possible effects of time variation on the spectrum in Fig. 1 can be confirmed or eliminated. The simultaneous observations at 2,695 and 8,085 MHz do show signs of the high frequency turn-up clearly indicated a few weeks later at 10,630 MHz.

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Mineralogy of Apollo 15415 "Genesis Rock": Source of Anorthosite on Moon

PETROGRAPHIC, microprobe and X-ray data were obtained from thin section 15415,14 and 1-2 mm fines 15415,28, part of the anorthositic rock returned by Apollo 15. The section consists of ~97% coarse (1-4 mm) plagioclase and ~3% pyroxene associated with a trace of ilmenite. The pyroxene occurs as small (~0.05 mm) blebs both within and between plagioclase grains; in addition, several larger (~0.6 mm) pyroxene grains occur along boundaries. The fines consist of ~98% plagioclase with the rest being glass spheres and soil particles. Electron microprobe analyses were made of ten plagioclase points and ten pyroxene grains using standard procedures¹.

Table 1 Pyroxenes; wt. % Oxides; Mol % End Members

	Group 1		Group 2 *	
	No. 1	No. 2	Average	Range
Na ₂ O	0.0	0.0	0.03	0.01-0.04
MgO	19.6	19.8	14.0	13.7-14.3
Al ₂ O ₃	0.63	1.43	1.32	0.97-1.51
SiO ₂	51.0	51.7	52.2	51.7-52.6
CaO	1.16	1.70	21.6	20.8-22.8
TiO ₂	0.24	0.20	0.54	0.39-0.70
CrO	0.15	0.14	0.22	0.19-0.26
MnO	0.50	0.51	0.26	0.23-0.31
FeO	27.2	26.6	9.1	8.0-10.0
Sum	100.5	102.1	99.3	98.2-100.1
En	55	55	40	39-41
Wo	2	3	45	44-47
Fs	43	42	15	13-16

* Data for eight analyses averaged.

The plagioclase analyses show an unusually high average An content of 97.6 (range—An_{96.7} to An_{99.0}), while minor elements have uniformly low concentrations, K 0.02, Fe 0.095, and Mg 0.035 per cent by weight. A single crystal from the fines showed sharp (b) and (c) X-ray diffractions characteristic of primitive anorthite. Polarized optical study of the thin section showed frequent, irregular twinning of the plagioclase, whose boundaries moved under pressure from a needle. Such elastic mechanical twinning is characteristic of anorthite². Probably the irregular optical extinction and at least some of the twinning developed from mechanical deformation at the Moon's surface.

The pyroxene analyses consist of two distinct groups (eight augites and two low-Ca pyroxenes of undetermined symmetry) each with little compositional variation (Table 1). X-ray scanning images for FeK_α and CaK_α showed no detectable intergrowths in the larger pyroxenes, but one of the smaller blebs consisted of an intergrowth 10 μm in scale as shown by the Fe scanning image of Fig. 1.

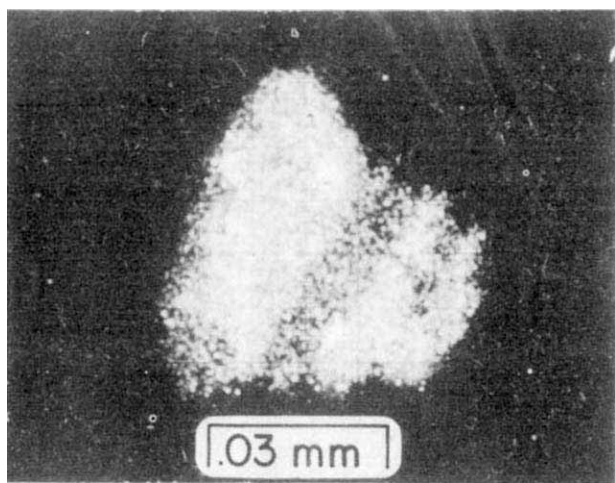


Fig. 1 FeK_α X-ray scanning image of pyroxene intergrowth. Light colour, low-calcium pyroxene; medium-light, high-calcium pyroxene; black, host plagioclase.

Fig. 2 is a plot of the normative constituents CaSiO₃ (Wo), MgSiO₃ (En) and FeSiO₃ (Fs) for the pyroxenes with respect to composition ranges found for Apollo 11, 12 and 14 specimens. The composition gap is greater than for any other pair of coexisting pyroxenes in a holocrystalline rock yet found on the Moon. Because the pyroxenes consist largely of separate grains, this suggests crystallization (or recrystallization) at a relatively low temperature with respect to the mare basalts. Rather than surface volcanism, one must look to deep-seated plutonic or to metamorphic processes.

The plagioclase is more calcic than any other yet found for holocrystalline rocks on the Moon, and both its major and minor elements agree well with a prediction made on the basis of studies of plagioclase from Apollo 11 and 12 rocks³. Fig. 3 summarizes the variation found between weight % Fe and mol % Ab (NaAlSi₃O₈) in plagioclases from mare basalt and exotic material from the fines (the latter probably corresponding to much of Apollo 14 material). Smith noted³ that the data areas appeared to diverge from a composition near An₉₇Ab₃: K 0.03, Fe 0.1, Mg 0.01 weight %, a value consistent with that for rock 15415. He stated that "... it is tempting to speculate that the above composition may represent a source material common to all populations of both Apollo 11 and Apollo 12 material, while more sodic varieties represent the products of crystal-liquid differentiation under plutonic and volcanic conditions further modified in some instances by metamorphism".

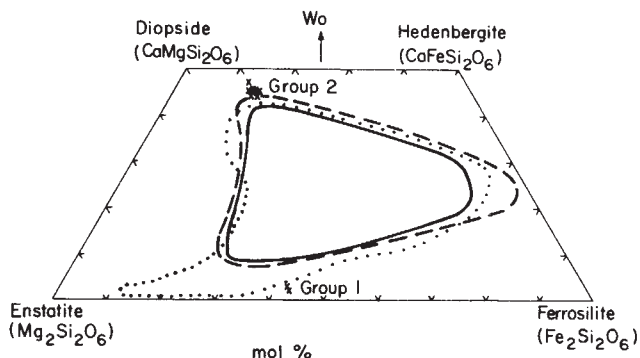


Fig. 2 Generalized plot of pyroxene compositions for Apollo 11 (---), 12 (—) and 14 (···) from many sources. Pyroxene analyses from 15415, 14 are indicated by crosses.

If rock 15415 represents an early differentiate of crystal-liquid fractionation producing feldspar-rich rocks from pyroxene-rich magma, one would expect the pyroxenes to be Mg-rich. The pyroxenes from 15415 are indeed more Mg-rich than the majority of pyroxenes from mare basalts, but they are less Mg-rich than some others, notably those from fines and exotic fragments. Perhaps some of these result from an earlier stage of differentiation, before plagioclase began to crystallize, while others result from late-stage accretion.

The discovery of plagioclase-rich fragments in Apollo 11 fines led to suggestions of extensive crystal-liquid differentiation producing an anorthositic crust⁴ or a lunar crust composed of a mixture of plagioclase-rich rock, basalts and minor ultramafic material⁵. No evidence of cumulate textures has yet appeared to support these suggestions which require that plagioclase crystals float in a basaltic liquid. The plagioclase in 15415 does not show cumulate texture either. Perhaps metamorphism has obliterated earlier textures, but we wish to quote other evidence that argues against Earth-type crystal-liquid differentiation as the source of the plagioclase-rich fragments in Apollo 11 fines. For terrestrial igneous intrusions of basaltic composition, the NaAlSi₃O₈ content of the plagioclase increases with the Fe₂SiO₄(Fa) content of the coexisting olivine as shown for four intrusions listed in ref. 6 (Fig. 4). Five fragments from Apollo 11 listed in ref. 7 show a trend sloping in a quite different direction, with Fa of the olivine decreasing as Ab increases in the plagioclase. The olivine and plagioclase solid solutions are supposed to be nearly ideal at liquidus temperatures, so there is no simple explanation of this trend on the basis of crystal-liquid fractionation analogous to that seen in terrestrial intrusions. One possibility is extensive

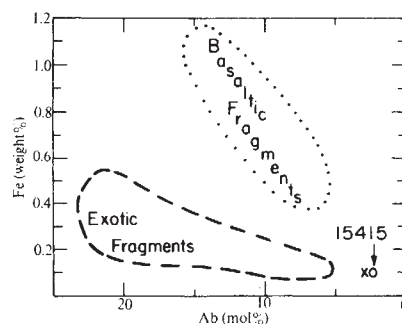


Fig. 3 Generalized plot of Fe (weight %) versus Ab (mol %) for Apollo 12 rocks. Dashed area, breccia and grey-mottled fragments; dotted area, basaltic fragments 12070, 145 and 12010, 31. Apparent intersection marked by cross, observed composition in 15415, 14 by circle.

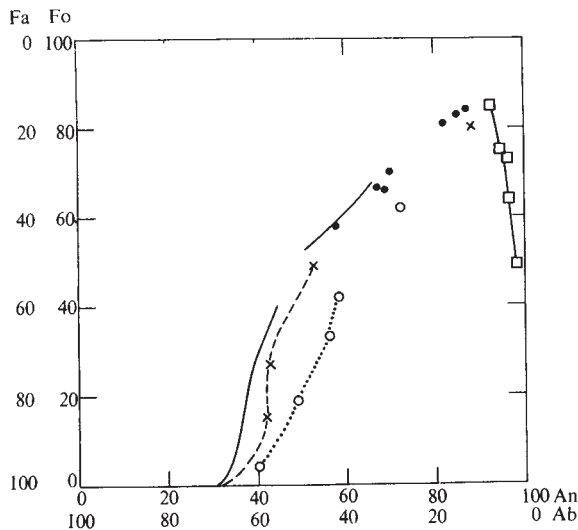


Fig. 4 Ab content (mol %) of plagioclase against Fa content (mol %) of coexisting olivine in terrestrial igneous intrusions of basaltic composition and in plagioclase rich fragment from Apollo 11 fragments. —, Skaergaard; x, Buchveld; ○, Insch; ●, Cullin; □, Apollo 11.

volatilization from lava lakes⁸ which should deplete the sodium in preference to the calcium, perhaps while the content of ferrous iron was increasing in the liquid.

At this time, it is obvious that the feldspar-rich rocks from the Apollo 11 mission pose difficult problems, and it remains to be seen whether rock 15415 is correctly named the "genesis rock".

We acknowledge support from NASA.

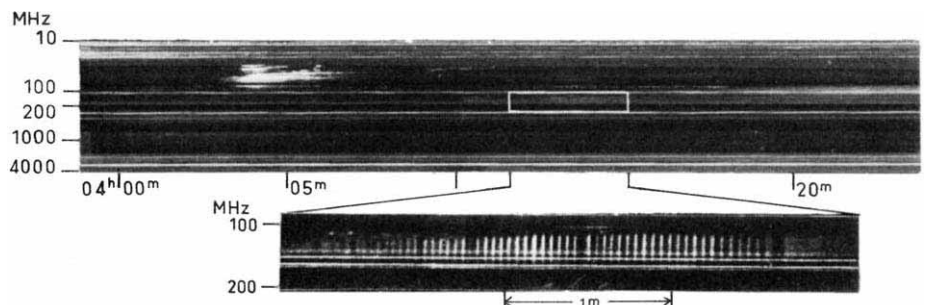
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Fig. 1 Dynamic spectrum record of the pulsed event of September 27, 1969. A type II burst is clearly visible at the start of the event, and the second harmonic continues faintly at frequencies less than 60 MHz during and after the pulsed part of the event. The pulses occur in the part of the record enclosed by a white box and a high contrast enlargement of this section of record is reproduced in the bottom half of the figure to show the pulses more clearly.



Regular Pulses from the Sun and a Possible Clue to the Origin of Solar Cosmic Rays

A CURIOUS but rare feature of the metre-wave continuum (type IV) radiation received from certain large solar flares is the pulsating structure which modulates the intensity in a periodic or quasi-periodic manner^{1,2}. The modulation may persist for about 1 min or more and the period of the pulsation is typically of the order of 1 s. Of various explanations suggested, we consider the most satisfactory to be that of Rosenberg, in which the radiation is attributed to synchrotron radiation emitted by electrons in a magnetic flux tube embedded in the solar corona and the pulsations are attributed to modulation by standing magnetohydrodynamic (MHD) waves set up within the tube. We now present further evidence of this phenomenon and outline a model which accounts both for the acceleration of the emitting electrons and for the pulsations themselves. There is also evidence to suggest that energetic protons may be accelerated by the same process. We consider that the phenomenon affords a possible observational clue to a physical process by which solar cosmic rays can be generated high in the solar corona.

Our work was stimulated by an extraordinary pulsating event recorded with the Culgoora radiospectrograph on September 27, 1969 (Fig. 1). A remarkably regular series of about 50 sharp pulses were received in the frequency range 100 to 200 MHz, each pulse occurring almost simultaneously throughout the frequency range. The interval between pulses varies slowly from 2.5 to 2.7 s during the lifetime (2.5 min) of the pulse train. The pulses appear as a deep modulation of the middle part of an otherwise smooth rise and fall of continuum (Fig. 2).

The pulses begin 25 min after the start of a large flare. The production of a type II burst (Fig. 1) signifies³ the generation of a shock wave and its passage through the corona. Because the fundamental band of the type II burst had, at the time of the pulsations, drifted down to a frequency of about 30 MHz, the shock wave was then at a height of about 1.5 $R_{\odot}$.

A search through our records revealed seven other instances of pulsations. All but one were accompanied by type II bursts and occurred at a time when the shock wave had reached a height of between 1 and 2 $R_{\odot}$.

In an effort to interpret this phenomenon, we have sought a physical model which accounts for (1) the extreme regularity and sharpness of the pulses; (2) the fact that the pulses modulate part of a longer rise and fall of continuum; and (3) the occurrence of the first pulses at the time that a shock wave passes through a height level of $\geq 1 R_{\odot}$. The most plausible model is illustrated in Fig. 3. We presuppose the existence of a well defined magnetic flux tube with its feet in the photosphere and its top high in the corona; several pieces of radio and optical evidence point to the formation of such magnetic arch structures or loops above flare regions.

The shock wave from the flare expands and at some stage interacts with the flux tube (Fig. 3a). The shock front compresses the magnetic field in the two regions where it crosses

the flux tube and generates large amplitude Alfvén wavetrains which travel up and around the loop in each direction. We assume that the magnetic field inside the loop is so much greater than the field outside the loop that the Alfvén waves travel several times faster than the shock itself. Thus the length of the tube above the shock soon becomes filled with the intermingled pair of oppositely directed wavetrains. This physical situation is one suited to the acceleration of electrons by the Fermi process as discussed by Parker⁴ and Wentzel⁵. The electrons gain energy at repeated reflexions between converging waves, the pitch-angle distribution of the electrons being maintained by scattering on the sharp crests which develop on waves with large amplitudes. The increasingly energetic electrons at the top of the arch become the source of synchrotron radiation of increasing intensity and so account for the initial rise in the level of continuum radiation.

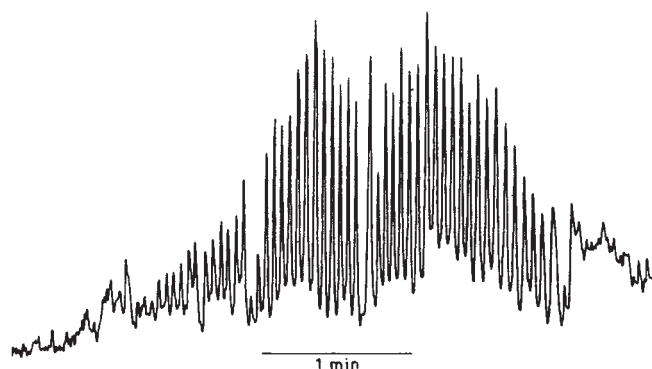


Fig. 2 Microphotometer trace along the spectral record of Fig. 1 showing the variation with time of the intensity of radiation received at 150 MHz.

A new situation can develop when the shock front reaches the top of the arch (Fig. 3b), for then the front can be aligned nearly parallel to the flux tube over a length which is large compared with the tube diameter. Under this condition the tube is excited into radial oscillations of the kind discussed by Rosenberg², the magnetic field oscillations giving rise to oscillations of the intensity of the synchrotron source. We have made calculations which demonstrate that small variations in the magnetic field can produce considerably larger variations in the intensity of synchrotron radiation. The steep dependence of intensity on magnetic field thus allows the generation of sharp, deeply modulated pulses even if the magnetic oscillations are sinusoidal and relatively weak.

After the shock front has cleared the loop (Fig. 3c) the energetic electrons are gradually lost from the source as they diffuse back down the field lines towards regions of higher

density where the medium suppresses the synchrotron emission. During this phase there is a gradual decay of the continuum.

The transition from pulsations to final continuum is very abrupt, and the continuum seems to be continuous with the envelope of pulse maxima. With the possible exception of these two puzzling details, we believe that we have explained all the basic features of this burst.

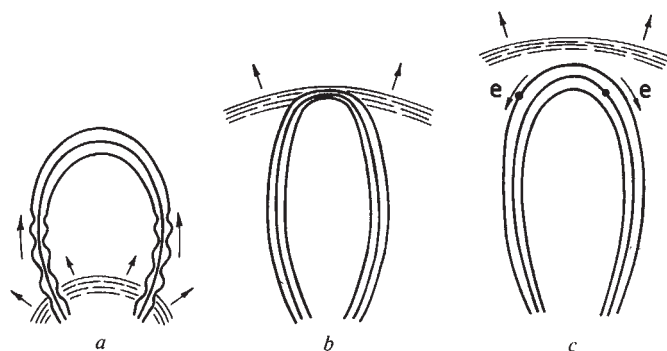


Fig. 3 Diagrams illustrating the geometry of the mechanism proposed to explain the event of Figs. 1 and 2. The three diagrams represent successive stages of the upward expansion of a shock wave and its interaction with a discrete magnetic flux tube.

This model can be explored quantitatively with the aid of several important observable parameters relevant to the maximum phase of the pulsations, namely the period of the pulsation τ , ≈ 2.5 s; the plasma frequency (from type II burst) $f_p \approx 30$ MHz; the peak frequency of synchrotron emission f_m , ≈ 150 MHz; and the maximum flux density S , $\approx 5 \times 10^{-21}$ W m⁻² Hz⁻¹, measured at the frequency f_m .

If d is the diameter of the flux tube, l the effective length of the tube contributing to the pulsations, T_B the peak brightness temperature of the source, E the kinetic energy of the radiating electrons (assumed mono-energetic), $f_B = eB/2\pi m_0 c$ the mean electron gyro frequency and $v_A \approx 7 \times 10^3 f_B/f_p$ the Alfvén wave velocity, we may make use of the relations

$$\begin{aligned} \tau &\approx d/v_A \\ kT_B &\approx 0.5c^2 D^2 S/(ldf_m^2) \\ E &\gtrsim kT_B \end{aligned}$$

where D is the distance between the Sun and the Earth and k is Boltzmann's constant. We also make use of an approximate form⁶ of the formulae for synchrotron radiation to relate f_m to E and f_B and f_p . Assuming $l \approx 10d$ we have derived, with the aid of some numerical computation, the following

Table 1 Comparisons with Solar Proton Observations

Date	Time of maximum (UT)	Flare Coordinates	Imp.	Cosmic-ray increase Date	UT	Delay (h)
June 27, 1960	0010	S10 E33	3	No data		
February 24, 1969	2316	N12 W32	2B	February 25	1000 to 1100	(~11)*
September 27, 1969	0412	N09 E02	3B	September 27	0900	5
April 8, 1970	2333	N15 E55	SN	No increase		
June 30, 1970	0316	N18 E56	SN	No increase		
November 5, 1970	0320	S12 E37	3B	November 5	0200 to 0800	< 5
December 11, 1970	2215	N16 W00	2N	December 12	0900	7
January 25, 1971	2309	N19 W49	2B	January 25	2366	0.5

* A second flare starting at 0903 on February 25 was a more likely cause of this proton event. Apparently the second flare was associated with the pulsed radio event described by Rosenberg².

quantities: $d \gtrsim 0.02 R_{\odot}$; $E \lesssim 0.8$ MeV; $B \gtrsim 6$ gauss; $v_A \gtrsim 4 \times 10^3$ km s $^{-1}$; $T_B \lesssim 10^{10}$ K. All these values seem to be within reasonable bounds if it is appreciated that the somewhat high value of magnetic field refers to the highly localized resonating flux tube, which is likely to contain strong electric currents and twisted fields.

Further important considerations were suggested by the model—for example, the Fermi process invoked to accelerate the electrons may also be effective in accelerating protons in the same region. To test this idea we examined the reports of satellite observations of solar protons⁷ for all eight pulsating events recognized from our data (see Table 1). Four of the seven events for which proton data were available were associated with proton emission and, in a fifth case, there is a possible association. The other two were at large eastern longitudes and were thus unfavourably located for the detection of protons. We consider that this result represents *prima facie* evidence for an association between the radio pulsations and the acceleration of protons. The same basic particle accelerator that we are proposing—that is the interaction of a shock or other MHD wave with a discrete arch-shaped magnetic flux tube—may explain why synchrotron sources are seen—on radioheliograph records—to become concentrated at the top of magnetic arches⁸. A similar mechanism may also be responsible for the acceleration of particles at lower heights in the solar atmosphere and, indeed, for other astrophysical phenomena.

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What Flux Limits can be Set for X-ray Pulses accompanying Weber's Pulses?

THE vast ratio, $\sim 10^{-40}$, between gravitational and electromagnetic forces has prompted two groups^{1,2} to search for radio pulses which might accompany the pulses reported by Weber^{3,4}. In view of the restricted bandwidths in the radio experiments, and uncertainties about the dispersion in the interstellar plasma, I discuss here the sensitivities that might be attained in other regions of the electromagnetic spectrum.

X-ray satellites⁵ could in principle be used to look for occasional bursts of X-rays, but with an expected event rate of ~ 1 day $^{-1}$ (ref. 4), it is unlikely, however, that they could be spared for the necessary long periods of observation. Moreover, many of the satellite instruments have narrow beams, and use spin and precession to achieve all-sky coverage.

This letter draws attention to the potential of the upper-air X-ray fluorescence technique⁶⁻⁹, which is ground-based, cheap, has a wide input energy bandwidth, and is non-directional. The latter feature is particularly important, as the "beamwidth" of

Weber's existing detector is $\sim 70^\circ$ (ref. 4). How small a fraction of the energy in the pulses of gravitational radiation (GR) would have to be emitted in the X-ray band to be detectable by this method, assuming that GR events arise from collapsing objects at the galactic centre? The question of the time-scale is vital. A collapsing object of mass $\sim 10 M_{\odot}$ would emit a GR pulse of duration ~ 0.1 – 1 ms¹⁰, but the emission of any electromagnetic radiation would in general be much longer, arising, as it must, from the outer regions of the object. On the shock-wave model of supernovae⁷, however, prompt X-rays are expected on exceedingly short time-scales, $\sim \mu$ s. Several models of stellar collapse¹¹⁻¹³ suggest that the bulk of the prompt emission of energy from a typical collapsing star emerges on a time-scale in the region 0.1–3.0 s.

Consider a single large phototube of area A and quantum efficiency, ϵ_p , viewing the entire (2π) solid angle of sky, set up to detect an X-ray burst of flux-level ϕ_x through the 3914 Å fluorescence band of the N_2^+ ions in the upper atmosphere. If the fluorescence conversion efficiency is ϵ_f , and the integration time constant τ is arranged to match the duration of the burst, the signal to noise ratio (S/σ) is given by¹⁴

$$(S/\sigma) = (\phi_x \epsilon_f / 2h\nu_{3914}) \cdot (A\epsilon_p / \phi_B \tau)^{1/2} \quad (1)$$

where ϕ_B is the background light from the night sky, integrated over the hemisphere.

Inserting $\phi_B = 1.55 \times 10^9$ photons s $^{-1}$ (3500–5000 Å) (ref. 15), $A = 730$ cm 2 , $\epsilon_p = 0.15$ (S-11 cathode), $h\nu_{3914} = 3.1$ eV, and $\epsilon_f = 10^{-3}$ (ref. 16) (the average value over $E_x \sim 10$ keV–100 keV) in (1), integrating over $\tau = 0.1$ s, and demanding a signal $S = 15 \sigma$ (that is, roughly three times peak-to-peak noise), the limiting detectable X-ray flux is

$$\phi_x = 1.8 \times 10^{-4} \text{ erg cm}^{-2} \text{ (event)}^{-1}, \text{ in the band } 10\text{--}100 \text{ keV} \quad (2)$$

If we take Weber's result to indicate a GR-flux $\sim 10^4$ erg cm $^{-2}$ (event) $^{-1}$ in his bandwidth, then an associated X-ray burst would escape detection in this exceedingly simple detector, only if

$$\phi_x \leq 1.8 \times 10^{-8} \phi_{GR} \quad (3)$$

The intrinsic input bandwidth of a fluorescent receiver is 100 eV–100 keV (ref. 9), but photoelectric absorption in the interstellar medium will eliminate the lower energy regions. Taking a column density $\int n_H dl = 1.5 \times 10^{22}$ atoms of atomic hydrogen cm $^{-2}$ toward the galactic centre¹⁷ ($d = 8.2$ kpc), and the absorption spectrum of Bell and Kingston¹⁸, the opacity of the interstellar medium to the galactic centre is unity for $E = 1.7$ keV. Taking a conservatively lower energy limit of $E = 5$ keV, we thus ensure that the absorption is insensitive to the abundances of H $_2$, He or Ne, about which there is still some discussion¹⁹; Compton scattering is also negligible¹⁹. There may also be a local dense cloud around the site of Weber's reported events which would yield a higher than average column density.

Scattering by dust causes both attenuation and time dispersion of X-ray pulses from distant sources²⁰, and is more difficult to assess, but some tentative estimates of time-dispersion can be made from existing observations of X-ray sources near the galactic centre. Absorption and scattering cannot be too severe, for at least eleven point sources have already been discovered in the direction of the galactic centre²¹, and their angular diameters are $< 1.5'$. Assuming that this figure represents an upper limit to the diameter of a halo caused by dust scattering, and using the nomenclature in ref. 20, then $\theta \sim 3'$, at the geometric mean energy 3.3 keV of the energy band used by the MIT group²¹.

Extrapolating to the geometric mean energy of the proposed fluorescent detector, that is 22 keV (for 5–100 keV) I deduce, since $\theta \propto \lambda$, the corresponding scattering angle $\theta \sim 1.6 \times 10^{-5}$ radians, so that the time dispersion δt , again from ref. 20, is $\delta t \sim D\theta^2/32c$. With $D = 8.2$ kpc, $\delta t \sim 6.6$ s. Increasing τ from 0.1 s to 7 s, in (1), the sensitivity is lowered by $\sqrt{70}$, that is, by

roughly one order of magnitude; sky transparency fluctuations may well then set the limit of performance on such a time-scale. The above arguments necessarily depend on the composition, dimensions, and number-densities of the particles involved.

In spite of this estimate, however, if the optical extinction coefficients are any guide, the effects of dust scattering may be more severe. It has been estimated²² that in the visible region $A_v = 2$ mag for the pulsar NP 0532 at $D = 2$ kpc, while for the galactic centre ($D = 8.2$ kpc), A_v may be as large as 25 mag (ref. 23), or even 29 mag (ref. 24), if the extrapolations from the infrared are reliable. The relevance of these figures to the present discussion on X-ray scattering nevertheless depends critically on the sizes of the particles or grains.

There is already evidence^{14,25} that light pulses of unknown origin are detected from the night sky, on time-scales $\sim 50 \mu\text{s}$ –1 ms, though such light receivers have not yet been operated with the much larger integrating times (~ 0.1 s) suggested here.

When lists of the times of occurrence of GT events are published by Weber or others, a single night-sky fluorescent receiver may be sufficient to set a low limit on the X-ray flux accompanying these events. In the absence of such published data, however, more complicated installations would be necessary, involving widely spaced light receivers operating in coincidence. To observe the galactic centre with reasonable efficiency, these ground-based X-ray experiments should be carried out in the southern hemisphere or at low latitudes in the northern hemisphere, at desert or mountain sites, which are free from interference from a.c. lighting and man-made sources of pulsed light.

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BIOLOGICAL SCIENCES

Electron Density Profiles of Nerve Myelin

THE structure of the nerve membranes within the myelin sheath of frog sciatic nerve has been studied by low-angle X-ray diffraction. Many additional orders of diffraction have been recorded from nerve, and, from a structure analysis of this new X-ray data, a twelve-parameter electron density model is proposed. Fourier series representations of the one-dimensional electron density of live nerve myelin at two different resolutions are also presented; these resolutions are 7 Å and 4.8 Å.

It has been known for some time that the low angle X-ray diffraction pattern of peripheral nerve myelin^{1,2} shows the first five diffraction orders ($h=5$) of a radial repeat distance $d=170$ –185 Å depending on the variety of nerve. The radial repeating unit is derived from two plasma cell membranes which form the membrane pair. The interpretation of the low angle X-ray diffraction intensities from nerve leads to a description of the one-dimensional electron density distribution in a radial direction at right angles to the surface of the myelin sheath. The effective resolution Δx of a Fourier series representation of this electron density is given by $\Delta x = d(2h)^{-1}$ where d is the radial repeat distance and h the number of diffraction orders used in the synthesis. The low angle X-ray diffraction pattern of frog sciatic nerve^{1,2} had $d=171$ Å, $h=5$, and hence the effective resolution is only moderate, namely, $\Delta x=17$ Å. Many additional orders of diffraction, $h=18$, have been recorded, however^{3,4}, and the effective resolution of a Fourier synthesis is now considerably better as $\Delta x=4.8$ Å.

This resolution will only be meaningful if the correct phase can be found for each order of diffraction. Fortunately, the radial repeating unit seems, from the way the myelin sheath is generated from the Schwann cell membranes, to have a centre of symmetry. This means that the phase of each diffraction order can only be + or -. Thus, there are 2^h different ways of assigning phases to the h orders of diffraction. Different methods of structure analysis have been used at various times in an attempt to solve the phase problem and so obtain a valid description of nerve myelin structure. These methods are as follows: (1) swelling experiments to trace the Fourier transform⁵⁻⁹; (2) model building to choose between certain kinds of possible electron density models^{7,9-11}; (3) examination of Patterson difference function¹¹; (4) examination of Fourier difference densities; (5) the use of the sampling theorem to examine two or more closely related sets of X-ray data from nerve, and the use of the sampling theorem as a method of analytic continuation¹²; (6) examination of the X-ray patterns from swollen and shrunken frog sciatic nerve⁸.

We have developed a twelve-parameter electron density model¹⁵ for nerve, in which we use the following notation: d , radial repeat distance; v , thickness of the membrane pair; c , thickness of the cytoplasmic fluid layer composed of electron density F ; $d-v$, thickness of the extracellular fluid layer composed of electron density F ; l , thickness of the layer composed of electron density L ; i_1 and i_2 , thicknesses of the layers composed of electron density I ; p_1 and p_2 , thicknesses of the layers composed of electron density P ; s , thickness of the layer composed of electron density S . The electron densities have the

Table 1 Model Phases for the First Twelve Diffraction Orders

Kind of model	$h = 1$	2	3	4	5	6	7	8	9	10	11	12
Five-parameter	—	+	+	—	—	+	+	—	—	+	+	+
Seven-parameter	—	+	+	—	—	+	+	—	+	—	—	—
Eight-parameter	—	+	+	—	—	+	+	—	+	—	—	—
Twelve-parameter	—	+	+	—	—	+	+	—	+	—	—	—

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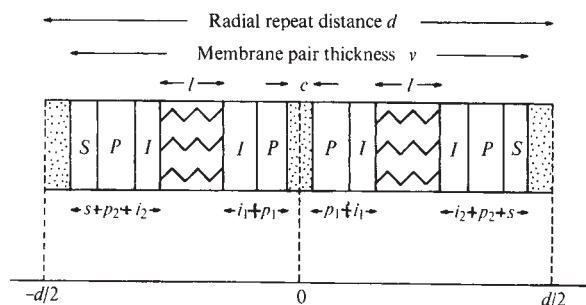


Fig. 1 The twelve-parameter electron density model is centrosymmetrical and contains two asymmetric nerve membrane units per radial repeat. The clear regions refer to electron densities P , I and S , the zigzag lines refer to electron density L and the dotted regions refer to the fluid electron density F . The thickness of a single nerve membrane unit is given by $p_1 + i_1 + l + i_2 + p_2 + s$.

following variation: P is high, I is moderately high, S is moderate whereas L is low. The twelve parameters are the five electron densities (F , P , I , L , S) and the seven layer thicknesses (c , p_1 , p_2 , i_1 , i_2 , l , s) but, because fluid density F is known and because X-ray intensities are on a relative scale, there are only ten operational parameters. In order to describe electron densities in terms of electrons per $\text{\AA}^3$ additional considerations are required and have been described elsewhere^{9,13}. The following model parameters for frog sciatic nerve were obtained: $P=0.37$ electrons per $\text{\AA}^3$, $I=0.36$ electrons per $\text{\AA}^3$, $L=0.27$ electrons per $\text{\AA}^3$, $S=0.35$ electrons per $\text{\AA}^3$, $c=10$ $\text{\AA}$, $p_1=13$ $\text{\AA}$, $i_1=10$ $\text{\AA}$, $l=21$ $\text{\AA}$, $i_2=9$ $\text{\AA}$, $p_2=12$ $\text{\AA}$, $s=10$ $\text{\AA}$. A diagram of the twelve-parameter electron density model is shown in Fig. 1. The following properties of frog sciatic nerve myelin are noted. The thickness of a single membrane is 75 $\text{\AA}$, which is similar to that of earlier models. The single membrane is asymmetric and this is similar to that shown by the seven and eight-parameter models. The thickness of the central low electron density region is unexpectedly narrow (as in the three earlier models) and the actual value of l is 21 $\text{\AA}$; this region is thought to contain the lipid hydrocarbon chains. The thicknesses of electron density layers I and P have the property $i_1 \approx i_2$ and $p_1 \approx p_2$. The five layers therefore (p_1 , i_1 , l , i_2 , p_2) form an approximate centrosymmetrical unit. The asymmetry of the nerve membrane unit arises primarily because of the presence of the moderate electron density layer which is 10 $\text{\AA}$ thick and faces the extra-cellular fluid space. This observation of a symmetrical unit within the nerve membrane suggests that these five layers may constitute a symmetric lipid bilayer with the protein component

confined to only one layer, the 10 $\text{\AA}$ layer. Accordingly, a molecular model has been constructed and some of the details have been reported briefly¹⁵.

The phases of the first twelve reflexions for four models^{7,11,13,15} are shown in Table 1. The only difference is that the sign combinations of reflexions $h=9$ to 12 are reversed in the three later models. The strong $h=11$ reflexion has a negative phase in the three later models whereas it had the opposite phase in the 1968 model. A study using method (5) supports the choice of phases given by the later models. This study is independent of any model-building considerations. The Fourier series representation for nerve¹⁴ is given by the series

$$\left(\frac{2}{d}\right) \sum_l \{ \pm \} [J(h)]^{1/2} \cos 2\pi h x / d$$

where $J(h)$ is the corrected X-ray intensity and $\{ \pm \}$ refers to the phase information. Fourier syntheses calculated using $h=12$ and $h=18$ reflexions are shown in Figs. 2 and 3, respectively. The corresponding effective resolutions of these Fourier series are 7 $\text{\AA}$ and 4.8 $\text{\AA}$, respectively. The continuous curves are the Fourier series representations for the myelin layers of frog sciatic nerve; they were computed using the observed X-ray diffraction intensities after corrections had been applied and the phases from the twelve-parameter model. The discontinuous curves are the Fourier syntheses calculated using the theoretical diffraction derived from the model together with the model phases.

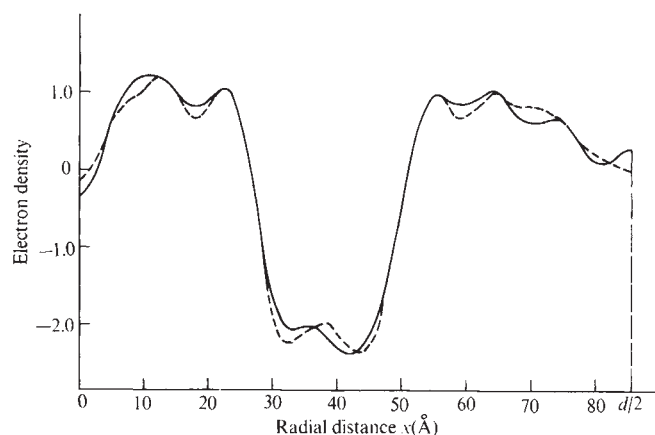


Fig. 3 Fourier series representations for the myelin layers of frog sciatic nerve computed using the first eighteen reflexions. The continuous curve refers to the observed Fourier series and the discontinuous curve refers to the calculated Fourier series. The Fourier syntheses are on the same relative scale.

To illustrate the agreement between the twelve-parameter model and the observed low angle X-ray data, it is convenient to show the corresponding Fourier series representations for live nerve. In Figs. 2 and 3 the observed and calculated Fourier syntheses ($h=12$ and $h=18$) show only small differences although the differences between the two electron density curves in Fig. 3 are more noticeable. The good agreement between the observed and calculated Fourier series suggests that the twelve-parameter model is a reasonable choice for nerve and therefore the parameters of this electron density model closely resemble the molecular parameters of live nerve.

It is appropriate to point out difficulties in trying to identify certain features of electron density curves with molecular parameters. For example, in Figs. 2 and 3, the Fourier series have a ripple contour superimposed on the true electron density of the nerve membrane; the wavelength of this ripple contour is approximately $2 \Delta x$. The fact that the interpretation of such a Fourier series is not rigorous and presents obvious problems has been recognized¹⁰. We have tried to avoid those difficulties

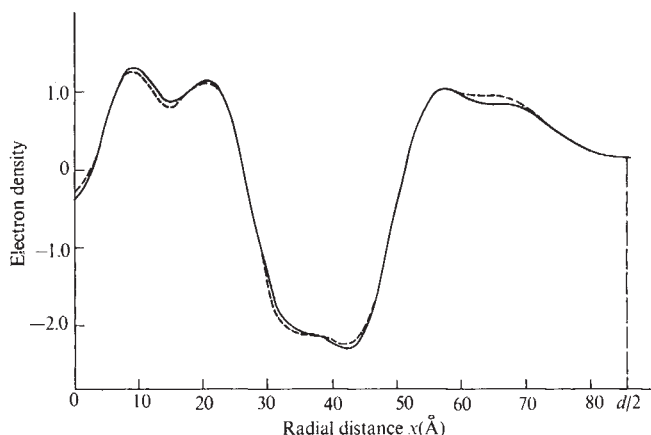


Fig. 2 Fourier series representations for the myelin layers of frog sciatic nerve computed using the first twelve reflexions. The continuous curve refers to the observed Fourier series and the discontinuous curve refers to the calculated Fourier series. The Fourier syntheses are on the same relative scale.

by starting with an electron density model. In this case the information contained within the observed Fourier synthesis can be examined by use of Fourier difference densities.

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Are Noradrenaline Excitations Artefacts?

It has frequently been reported that noradrenaline applied by microiontophoresis depresses firing in neurones of the central nervous system¹⁻¹¹. Excitatory responses have also been found, however, both in cells which are, and in cells which are not, depressed by noradrenaline¹²⁻¹⁹. In the former case, depression is followed by a delayed excitation. In all cases excitatory responses are delayed and often reach a maximum after the end of the application, after which the cell does not recover its original firing rate for 2-3 min. Furthermore, the excitant effects of noradrenaline are stereospecific for *l*-noradrenaline and can be blocked by the common adrenergic blocking agents^{12-14,18} whereas the depressant responses are not stereospecific and cannot usually be blocked by these agents^{2,5,8,12-14}. It has therefore been suggested that noradrenaline is an excitatory transmitter in the brain, and that the depressant effects represent a non-specific effect on cellular membranes or processes¹⁴.

We have found that microiontophoretic application of noradrenaline causes small blood vessels to constrict with a latency and time course strictly comparable to the excitant effects of noradrenaline on some central nervous neurones. The experiments were carried out on arterioles less than 500 μ in diameter of the intestine and mesentery of 300 g rats anaesthetized with urethane. Five-barrelled micro-pipettes were used for iontophoresis, and control experiments were carried out to check for pH or current effects. All drug solutions were 0.2 M in de-ionized water. Acetylcholine, acetyl- β -methyl choline, and sodium L-glutamate produced no apparent change of vessel diameter when ejected with currents of up to 300 nA.

Ejection of noradrenaline bitartrate produced a localized constriction of the vessels, the threshold for an observable effect on most vessels being at doses of about 20 nA. Maximal constrictions were obtainable with doses of approximately 100 nA. At intermediate doses an increase of ejecting current

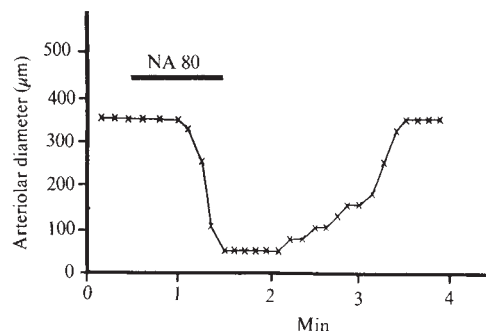


Fig. 1 A graph of the changes in the diameter of an arteriole against time as a result of an 80 nA dose of noradrenaline (NA80) applied by microiontophoresis. The long latency and slow recovery of the constriction are clearly seen.

increased the resulting degree of constriction. The changes in diameter of an arteriole resulting from an 80 nA dose of noradrenaline are shown in Fig. 1. The typically long latency of the effect (noradrenaline retaining current only 10 nA) and the slow recovery are clearly apparent. The peak effect is attained after ending the noradrenaline ejection. Similar observations have been made recently in the frog²¹.

We suggest that the neuronal excitatory effects of noradrenaline in some areas of the central nervous system may be secondary to effects on blood vessels. Indeed, it is not difficult to see a cause and effect relationship between vessel constriction and neuronal excitation. Constriction of a small blood vessel or capillary in the vicinity of a neurone soma would effectively reduce the availability of oxygen diffusing from the contained blood to at least a part of the cell. Furthermore, it has been known since the work of Lorente de N $\acute{o}$ ²² that hypoxia will depolarize nerve fibres. Hence it seems reasonable to assume that the localized hypoxia resulting from constriction of a small blood vessel would at least increase the tendency to depolarization of a nearby neurone.

This effect might be rather weak, however, in the case of larger cells which may be receiving oxygen from several nearby vessels. This might explain the observation that noradrenaline excitations are often not apparent until a burst of firing is initiated in the cell under study by, for example, an excitant amino-acid. In such cases the amine excitation is often seen as a prolongation of the amino-acid effect.

This hypothesis can also be used to explain certain differences seen by workers using different anaesthetics. In the cat neocortex, for example, Krnjević and Phillis^{7,20} using barbiturate-anaesthetized or unanaesthetized preparations observed depressant responses to noradrenaline normally, although higher doses occasionally elicited excitatory responses. Johnson *et al.*^{14,15}, however, noted excitatory effects of noradrenaline on 57% of the cells studied (compared with 20% depressed) during nitrous-oxide/halothane anaesthesia, and observed that administration of 0.5% halothane would potentiate excitatory responses of cells in barbiturate-anaesthetized animals, and would cause previously unresponsive cells in unanaesthetized animals to be excited by noradrenaline. Phillis and York⁹ in the same tissue observed a much smaller proportion of excitant effects (49% depressed) when using nitrous-oxide/methoxyflurane anaesthesia. Increasing the depth of halothane anaesthesia below a moderate level also reduces the incidence of excitant responses¹⁵.

Now, a study of blood vessel reactivity during anaesthesia²³ revealed that the response of small vessels to catecholamines is greatly enhanced during light halothane anaesthesia, is less during deep halothane anaesthesia, and is greatly reduced during methoxyflurane anaesthesia. Blood vessel responsiveness, therefore, correlates with the proportion of excitant responses seen with different anaesthetics.

The marked similarities between the pharmacology of noradrenaline excitation in the central nervous system, as mentioned earlier, and peripheral adrenergic pharmacology

lend further support to the hypothesis. Some results are also available for agonist studies. For example, ergometrine, which has negligible vasoconstrictor activity peripherally, has no excitant effects on central neurones. Methylethylergometrine, however, which does have vasoconstrictor activity also causes some excitation of central neurones²⁰.

Thus, some excitatory effects of microiontophoretically applied noradrenaline in the central nervous system may be indirect effects secondary to localized vascular changes. This is not to say that all such effects are produced in this way, but great care in the interpretation of microiontophoretic studies is essential.

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Serum-mediated Immunological Non-reactivity between Histoincompatible Cells in Tetraparental Mice

THE capacity of a serum factor, probably antibody or antigen-antibody complex, to block expression of cell-mediated immunity to tumours has been clearly demonstrated^{1,2}. This principle of blocked cellular immunity has been extended to account for the apparent tolerance between histoincompatible cells present in radiation³ and neonatally induced bone marrow cell chimaeras⁴. It has been suggested that even self-tolerance might be due, not to the absence of self-reactive lymphocytes, but to the presence of a serum factor capable of blocking the reactivity of these lymphocytes¹. Additional

support for this notion has been obtained using tetraparental (allophenic) mice. The mice are derived from the fusion of two eight-cell embryos, a stage long before the immune system has appeared. The fused embryo is reimplanted into a pseudo-pregnant female and matures into an apparently normal adult. If the parents are of different strains, a chimaeric animal develops whose tissues contain cells of both parental strains. These animals are functionally tolerant to themselves and either parental strain⁵. A microcytotoxicity assay has been used⁶ to demonstrate that there are lymph node cells in tetraparental mice which can kill parental strain cells *in vitro*, but the activity of which is presented by the presence of tetraparental serum. We have now extended the observation of blocking activity of tetraparental serum to mixed lymphocyte cultures (MLC) between parental strain cells. We also present preliminary results on the nature and specificity of the serum blocking factor.

Tetraparental mice were provided by Dr R. J. Mullen, Department of Neuropathology, Harvard Medical School. They were derived from the fusion of C57BI/10 and SJL embryos using techniques previously described⁷⁻⁹. All mice showed coat colour chimaerism and were more than 1 yr old. Normal C57BI/10, SJL, (C57BI/10 × SJL) F₁ hybrid, BALB/c and CBA mice were obtained from Jackson Laboratories, Bar Harbor, Maine. Sera were stored at -70° C and heat inactivated at 56° C for 40 min before use.

MLCs were carried out by the technique of Adler *et al.*¹⁰ with modifications (S. M. Phillips, C. B. Carpenter and J. P. Merrill, manuscript in preparation). Culture tubes contained either 15 × 10⁶ washed spleen cells of one strain, or 7.5 × 10⁶ cells from each of the two responding strains in a final volume of 2 ml. The medium was RPMI-1640 containing 10% heat inactivated normal human serum, penicillin, streptomycin, and hepes buffer. In cultures where only one of the two strains could undergo DNA synthesis (one way MLCs), 15 × 10⁶ spleen cells of the responding strain were incubated with 15 × 10⁶ mitomycin-treated spleen cells from the non-responding strain¹¹. Test sera were added to target cells 30 min before the addition of responding cells. The rate of DNA synthesis in each tube was assessed by adding 2 μCi of tritiated thymidine at 68 h of culture and determining its incorporation into DNA over the following 4 h. The proliferative response of spleen cells to phytohaemagglutinin (PHA) was measured at 48 h of culture. Tritiated thymidine incorporation was expressed either in c.p.m. or as an isotope incorporation index (III). The III for MLC was defined as

$$\frac{\text{c.p.m. in mixed cultures}}{\text{c.p.m. in unmixed cultures} \div 2}$$

and for PHA cultures as

$$\frac{\text{c.p.m. in cultures with PHA}}{\text{c.p.m. in cultures without PHA}}$$

Cytotoxicity assays were performed in 6 mm × 50 mm tubes. To each tube was added 50 μl. of a suspension of spleen cells labelled with ⁵¹Cr (5 × 10⁴ cells) and 50 μl. of either medium or test sera. The sera used included tetraparental, mixed parental, F₁ hybrid or monospecific anti H2 sera (C-2, C-19, C-33, obtained through the Transplantation Branch, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland). The tubes were incubated at room temperature for 15 min and 50 μl. of a 1 : 10 dilution of rabbit serum was added as a source of complement. The tubes were centrifuged 45 min later and the release of ⁵¹Cr determined and compared with that released from cells exposed to complement alone and from cells frozen and thawed four times. The maximum percentage of releasable ⁵¹Cr by each antiserum was calculated as:

$$\frac{{}^{51}\text{Cr released by cells exposed to antiserum} - {}^{51}\text{Cr released by cells in medium}}{{}^{51}\text{Cr released by frozen and thawed cells} - {}^{51}\text{Cr released by cells in medium}} \times 100\%$$

Table 1 Effect of Tetraparental Mouse Serum on Proliferative Response of Parental Strain Cells to PHA

Mouse strain	Serum	Isotope incorporation index	Significance level
SJL	—	28.5 ± 2.1	
	Tetraparental	22.7 ± 3.1	NS
	Mixed parental	21.9 ± 3.4	NS
	F ₁ hybrid	27.9 ± 1.9	NS
C57Bl/10	—	37.1 ± 3.5	
	Tetraparental	34.1 ± 3.6	NS
	F ₁ hybrid	39.2 ± 2.51	NS

Serum concentration was 1 : 20; the mean ± s.e. for four determinations is given. NS, Not significantly different from response in absence of added serum ($P > 0.05$).

Table 2 Effect of Tetraparental Mouse Serum on One Way MLC involving Parental (C57Bl/10 and SJL) and Third Party (CBA and BALB/c) Strain Cells

Responding cell	Target cell*	Isotope incorporation index †			Significance level, P §
		No serum	F ₁ hybrid ³	Tetra-parental serum ‡	
C57Bl/10	CBA _m	12.1 ± 1.6	14.5 ± 1.6	13.4 ± 1.9	NS
SJL	BALB/c _m	6.9 ± 0.9	7.3 ± 1.1	6.6 ± 1.3	NS
CBA	C57Bl/10 _m	5.6 ± 0.6	6.2 ± 0.8	2.3 ± 0.3	<0.001
BALB/c	SJL _m	6.7 ± 1.2	6.4 ± 0.9	2.1 ± 1.1	<0.07

* Target cells were rendered non-responsive by mitomycin (m) pretreatment.

† Mean ± s.e. of three determinations.

‡ Serum concentration was 1 : 20.

§ Comparison between control response in absence of added serum and response in presence of tetraparental serum.

The effect of tetraparental serum on the immunological interaction of parental strain cells was investigated. MLCs between C57Bl/10 and SJL cells were incubated in the presence and absence of tetraparental sera. Control cultures contained either a 1 : 1 mixture of parental sera or F₁ hybrid serum. Tetraparental serum at concentrations of 1 : 40 and higher significantly inhibited the MLC between parental cells (Fig. 1). At a concentration of 1 : 80 a small but significant stimulation was found. Control sera, except at the highest concentration tested (1 : 10), were without suppressive effect. The results depicted in Fig. 1 were obtained using a pool of sera obtained from seven tetraparental animals. Individual sera showed varying amounts of blocking activity.

The specificity of the inhibitory effect of tetraparental sera was determined in two ways. First, the response of parental strain cells to PHA was measured in the presence and absence of a concentration of tetraparental serum previously shown to inhibit the MLCs between parental strain cells. Tetraparental serum was without effect on this response (Table 1). Second, one way MLCs were established between parental strain (C57Bl/10 or SJL) and third party strain cells (BALB/c or CBA) (Table 2). Tetraparental serum did not inhibit the response of parental strain cells against mitomycin-treated third party target cells. Tetraparental sera, but not mixed parental or F₁ hybrid sera, did, however, significantly reduce the response of third party cells against mitomycin-treated parental strain cells.

Preliminary observations suggested that the blocking factor is directed against H2 antigens because cells differing from parental strain cells only at the H2 locus could not be blocked in the one-way MLC reaction (manuscript in preparation).

Tetraparental sera were therefore checked for direct cytotoxicity against parental strain cells in the presence of complement and also for their ability to block monospecific cytotoxic sera directed against H2 specificities present on parental cells (Table 3). The use of congenic strains in appropriate one-way MLCs has further shown that the serum blocking factor has specificity for the allelic products of the H2 locus (manu-

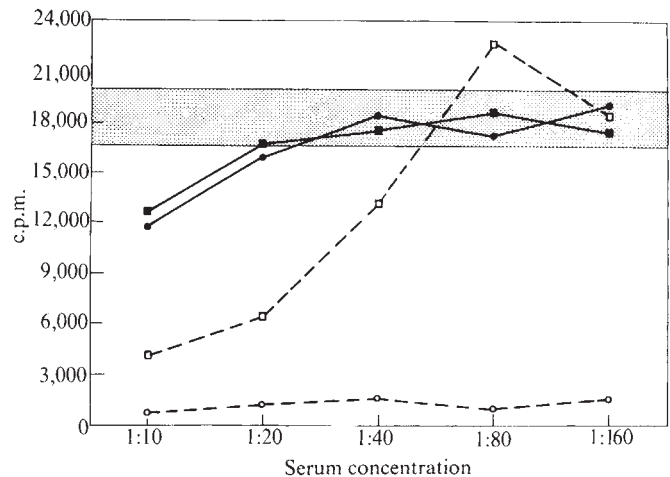


Fig. 1 Effect of tetraparental mouse serum on the incorporation of ³H-thymidine by MLC between parental strain cells. The shaded area represents the 95% confidence limits of ³H-thymidine incorporation in MLC in the absence of mouse serum. The incorporation of ³H-thymidine for control cells was taken as the mean incorporation of the two parental cells cultured separately. Each point represents the mean of four determinations. The average standard error of the mean was less than 10%. ○, Control cells; ●, normal F₁ serum; □, tetraparental serum; ■, mixed parental serum (1 : 1 V/V).

script in preparation). Tetraparental sera were not cytotoxic to parental strain cells. Further, preincubation of anti-H2 sera or prior exposure of target cells to tetraparental serum did not significantly reduce antibody-induced lysis.

Preliminary studies suggest that the blocking factor may be an immunoglobulin; it is insoluble in 35% saturated ammonium sulphate and can be removed from serum by the formation of precipitate with goat anti-mouse immunoglobulin serum.

Table 3 Effect of Tetraparental Mouse Serum on Cytotoxic Activity of Monospecific Anti-H2 Sera

Specificity of anti-H2 serum	Control	Per cent ± s.e. maximum ⁵¹ Cr release Anti-H2 serum preincubated with tetraparental serum	⁵¹ Cr-labelled cells preincubated with tetraparental serum
C-2	46.3 ± 3.2	48.6 ± 1.9	41.8 ± 2.3
C-33	56.3 ± 4.5	57.2 ± 2.9	47.5 ± 2.9
C-19	73.5 ± 4.9	67.0 ± 2.0	69.9 ± 3.7

Anti-H sera C-2 and C-33 detect specificities present on C57Bl/10 cells, while serum C-19 detects specificity on SJL cells. The antisera were tested on the appropriate target cell at a concentration of 1 : 100. A 1 : 50 dilution of anti-H2 sera was preincubated at room temperature for 60 min with an equal volume of a 1 : 30 dilution of tetraparental mouse serum.

⁵¹Cr-labelled target cells were exposed to a 1 : 30 dilution of tetraparental serum for 30 min at room temperature, before the addition of anti-H2 sera. Tetraparental serum was shown to have no direct cytotoxic effect on ⁵¹Cr-labelled target cells.

To determine whether the serum factor blocked spontaneous autoreactivity in tetraparental spleen cells, spleen cells from individual tetraparental, parental or F₁ hybrid mice were cultured in the presence of tetraparental, mixed parental, or F₁ hybrid sera (Table 4). Isotope incorporation was determined after 72 h. Tetraparental serum significantly reduced the level of blastogenesis by tetraparental cells but did not affect that of parental or F₁ hybrid cells. Control sera, F₁ hybrid and mixed parental, did not significantly suppress isotope incorporation by either tetraparental, parental or F₁ hybrid spleen cells.

Our results demonstrate the existence of a serum factor in tetraparental mice capable of blocking immune interaction between parental strain cells. In view of these and the earlier

Table 4 Effect of Tetraparental Mouse Serum on Spontaneous Blastogenesis of Tetraparental Mouse Spleen Cells

Animal	Radioactivity incorporated (c.p.m.)*		Reduction (%) due to tetra- parental mouse serum
	No tetra- parental mouse serum	1 : 20 tetra- parental mouse serum	
Parental	1,007 ± 172	942 ± 151	5.5
F ₁ hybrid	1,994 ± 307	1,884 ± 376	5.5
Tetraparental	3,472 ± 451	1,612 ± 198	53.6

Mixed parental and F₁ hybrid sera had no suppressive effect on the spontaneous blastogenesis of parental, F₁ hybrid, or tetraparental mouse spleen cells.

* Mean ± s.e. of four determinations.

results of a microcytotoxicity assay, it seems that immunological non-reactivity between the allogeneic cells of a tetraparental mouse is achieved, not by the elimination of self-reactive immunocytes, but by serum-mediated suppression of self-reactivity. Whether serum-mediated tolerance to self-antigens is also found in normal animals remains to be established. The absence of a factor in F₁ hybrid serum capable of suppressing MLCs between parental strain cells suggests that lack of autoreactivity against the principal H2 antigens in normal biparental animals is not serum-mediated. An immunocyte with antibody reactive with antigen present in the same cell might be destroyed; but where the immunocyte antibody is directed against self-components not present on the lymphocyte, this potential reactivity could be blocked by serum factors. Cohen *et al.*¹² showed that inbred rat lymphocytes preincubated with isogeneic fibroblasts *in vitro* could destroy a second set of such fibroblasts *in vitro*, as well as mediate a mild graft versus host reaction if given to newborn rats of the same strain. It therefore seems that the normal rat contains cells capable of recognizing antigens present on the animal's fibroblasts. It would be interesting to know whether the sensitization *in vitro* would still occur in the presence of autologous serum. The mechanism whereby serum factor blocks the MLC is unknown, and experiments are under way to test the various possibilities.

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Effect of Ethylene on Root Extension of Cereals

THE extension of root axes of barley is severely inhibited by concentrations of ethylene considerably lower than those which can occur in anaerobic soil¹; the sensitivity of this species has now been compared with that of three other temperate cereals and several varieties of rice from Nigeria, together with two dicotyledonous plants known to be particularly susceptible to injury from anaerobic soil conditions.

Young plants, with root axes about 10 cm long, were sealed through the gas-tight lids of 1,600 ml. cylindrical jars, with their roots in contact with filter paper which dipped into culture solutions in the bottom of the jars. The work was carried out in a controlled environment with a day length of 16 h and a light intensity of 18–20,000 lux; the temperature was maintained constant at 20° C for all species except rice, for which day and night temperatures were 25° C and 20° C respectively. After the roots had been in contact with the filter paper for 24 h, various concentrations of ethylene were applied; root extension was measured over the next 3 days, the concentrations of ethylene being monitored daily by gas chromatography¹.

The sensitivity of different species varied very widely (Table 1). Barley was the most sensitive of the temperate cereals and rye the least; some rice varieties were considerably more resistant than any temperate cereal. In Fig. 1 response curves for barley, rye and the most resistant rice variety (OS6) are compared. Concentrations of ethylene below 1 p.p.m. caused small increases in root extension in both rice and rye; a significant reduction (about 25% in rice and 40% in rye) occurred when the concentration was increased to about 10 p.p.m., but the magnitude of the effect was not increased by considerably higher concentrations (up to 350 p.p.m. with rice). In contrast, root extension in barley was not stimulated even at the lowest

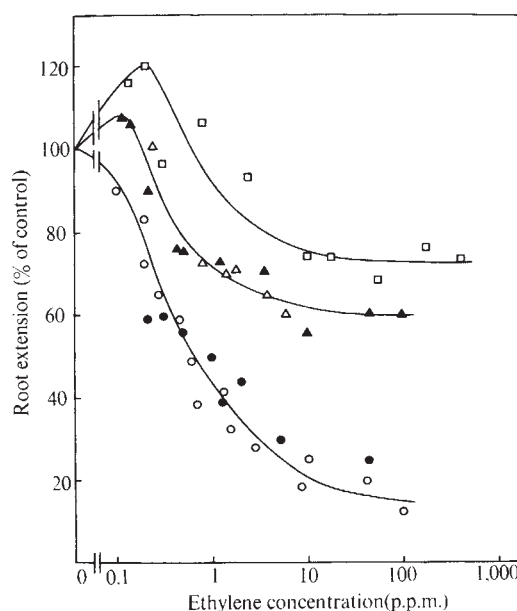


Fig. 1 The effect of ethylene on the extension of root axes of barley, rye and upland rice. Roots were exposed to ethylene for 3 days. □, Rice, OS6; ▲, rye, Ovari; △, rye, Lovasz Patonai; ●, barley, Proctor; ○, barley, Maris Badger.

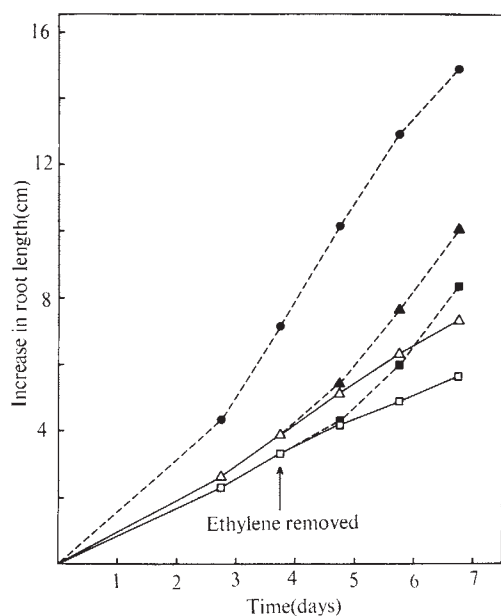


Fig. 2 Recovery of extension rate of barley roots after 4 days' exposure to sub-lethal concentrations of ethylene. Roots exposed to: $\blacktriangle$, 0.2 p.p.m. ethylene for 4 days; $\triangle$, 0.2 p.p.m. continuously; $\blacksquare$, 1.2 p.p.m. for 4 days; $\square$, 1.2 p.p.m. continuously; $\bullet$, control.

levels of ethylene, and 10 p.p.m. caused root extension to cease by the end of a 3 day period, a profusion of root hairs developing within 1–2 mm of the swollen apices. No anatomical abnormalities were observed at low concentrations which caused root extension to decrease by not more than about 50%; when ethylene was removed the normal rate of root elongation was then resumed within 1–2 days (Fig. 2). Although barley is more sensitive than any other cereal which has been examined, tomato and tobacco are still more affected, root extension being reduced to about one-quarter of the normal rate by 1 p.p.m. of ethylene.

Table 1 Effects of Ethylene on Root Extension of Cereals after Exposure for 3 Days

Species	Root extension (% of control)	
	1 p.p.m.	20 p.p.m.
Temperate cereals		
Barley (Maris Badger and Proctor)	45	20
Oats (Condor)	55	20
Wheat (Maris Widgeon)	70	60
Rye (Lovasz Patonai and Ovari)	75*	60
Rice		
SML 140/10	55	25
Mas 2401	75	50
BG 79	85	55
Mali Ong	75	50
Agbede	90*	75
OS6	100*	75

* >100% of control at 0.1–1 p.p.m.

No explanation is available for these interspecific differences but there is other evidence of the unusual response of rice to ethylene². Variations in the concentration of carbon dioxide up to levels which themselves reduce root extension do not affect the response of roots to ethylene. It has been observed that when barley seed has been stored in conditions which cause the percentage germination to decrease, the plants grown from the seeds which do germinate show an appreciably increased tolerance to ethylene.

Attention has recently been directed³ to the reduction in crop yields which results from inadequate drainage, and hence anaerobic conditions, in heavy soils in many parts of the

United Kingdom. It is therefore interesting that concentrations of ethylene capable of causing appreciable injury to temperate cereals can occur, apparently through microbial activity, when a wide range of soils are maintained in anaerobic conditions⁴. The view that ethylene deserves consideration among the causes of waterlogging injury is further encouraged by the fact that the temperate cereals fall into approximately the same order with respect to their tolerance to ethylene as to their survival of waterlogging under field conditions.

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Use of a Sustained-release Multiple Emulsion to Extend the Period of Radioprotection conferred by Cysteamine

PRACTICAL application of the substances which protect biological systems against ionizing radiation has been limited by their toxicity and because they are often metabolized so rapidly that they give protection only for a short time². We have incorporated the protective chemical cysteamine (mercaptoethylamine, MEA) in a sustained-release multiple emulsion³ in an attempt to extend the duration of protection in mice.

Cysteamine was injected intraperitoneally into female CS1 specific pathogen-free mice which were then irradiated at various times with 250 kVp X-rays filtered through 0.5 mm copper and 0.5 mm aluminium and delivered at a dose rate of 200 rad/min. Seven days later ^{59}Fe was injected intraperitoneally, and 3 days later the mice were killed. Blood was withdrawn from the heart and its ^{59}Fe content was measured to estimate total body erythropoiesis⁴; the spleen was weighed and fixed in Bouin's solution to render surface colonies (derived from haematopoietic stem cells) visible⁵. After doses of 350–500 rad, and in highly protected mice, colonies became confluent and therefore uncountable; the fraction of spleens producing confluent colonies was therefore used as the measure of colony formation.

Cysteamine was administered at a dose of 120 mg/kg body weight in aqueous solution, or at a dose of 340–400 mg/kg body weight when in the emulsion³ (formulated according to National Research Development Corporation patents 33255/67, 25146/68 and 56421/69). An 8% solution of cysteamine was slowly added to an equal volume of light liquid paraffin containing 10% of the detergent 'Arlacel 83' (sorbitan sesquileate) and homogenized in a Silverson blender. This was added to an equal volume of a 2% aqueous solution of 'Tween 80' (Honeywell Atlas Ltd) and shaken by hand to form the final multiple emulsion. The final stage of the emulsion had to be prepared within 30 min of administration; with longer intervals larger numbers of mice died because the emulsion degrades with time causing a more immediate release of cysteamine after injection, killing the mice. It is now possible, however, to prepare a more stable emulsion using 'Squalene' (BDH) and 'Arlacel A' instead of light liquid paraffin and 'Arlacel 83'.

We have compared radiation responses in irradiated mice protected by cysteamine with the responses in unprotected mice receiving 350 to 700 rad; this enables dose reduction factors to be estimated for the protected mice. If x rad produces the same

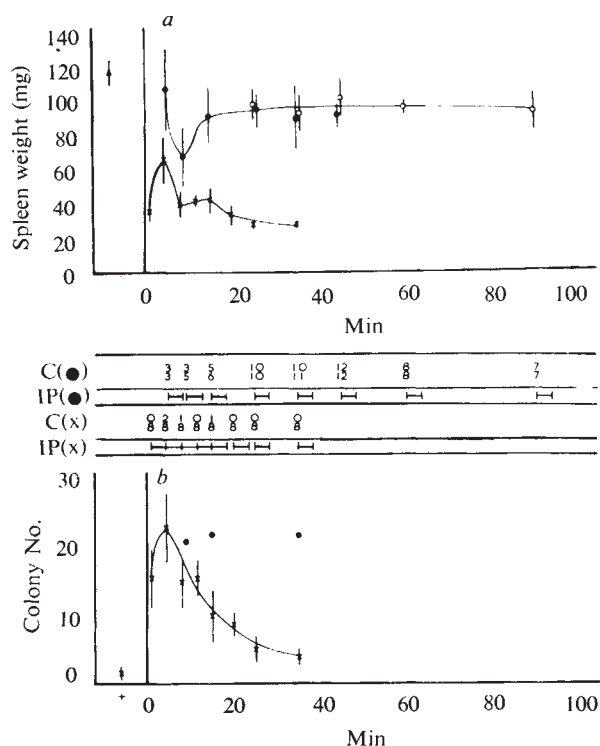


Fig. 1 Effect of cysteamine administered at various times before or after irradiation on mouse spleen weight and the number of visible colonies on the surface of mouse spleen 10 days after 700 rad total body irradiation. *a*, Spleen weight; *b*, spleen colony number, and fraction of spleens totally confluent at each irradiation time. Cysteamine in water, $\times$. Cysteamine in emulsion, $\bullet$. Sham irradiated controls, $\blacktriangle$. Cysteamine given after irradiation, $+$. C, Fraction of spleens totally confluent. IP, Irradiated period (3.5 min).

effect in protected mice as y produces in unprotected mice, then the dose reduction factor given by the protector is x/y . The parameters studied, which were spleen weight, colony counts and the percentage of spleens showing confluence, decreased progressively with increasing radiation dose in the range 350 to 700 rads.

When cysteamine was administered in aqueous solution, protection was maximum when it was given 7–10 min before 700 rad of total body irradiation, but had decreased to nearly zero when there was an interval of 20 min between injection and irradiation (Fig. 1). Thus significant protection is only given when irradiation takes place between 5 and 15 min after administration of the chemical, which is in accordance with previous findings. The dose reduction factors for the parameters examined did not exceed 1.7: even when the dose of protector was nearly lethal the dose reduction factor did not exceed 1.8 to 1.9.

When cysteamine was administered in an emulsion there was again a rapid increase in radioprotection during the first few minutes after injection (Fig. 1). This protection did not, however, decrease during the following 15 min; in contrast, it increased further and remained high for at least 1.5 h. In addition, the dose reduction factors estimated for the parameters spleen weight and colony count were significantly higher than those obtained when the cysteamine was administered in aqueous solution, for dose reduction factors greater than 2 were found up to 1.5 h after injection. Since all spleen colonies are confluent after doses of less than 500 rad, or in heavily protected mice, it was necessary to use a percentage of spleens that were totally confluent to estimate the dose reduction factor; this allows the estimation of dose reduction factors up to 2. Even using this system, however, it was only possible to define the dose reduction factor as being greater than two.

Uptake of ^{59}Fe into red cells was measured in some mice to give an estimate of total body erythropoiesis. Here again cyste-

amine incorporated in an emulsion conferred a high level of protection which was maintained over the period studied.

Mortality experiments were insufficiently precise for dose reduction factors to be estimated. It was clear, however, that considerable and prolonged protection against the lethal effects of X-irradiation also occurred, even when that irradiation took place 90 min after administration of the protector, since there was very little mortality in any of the protected groups (less than 15%), compared with 85% mortality in non-protected mice.

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New Method of Locomotion in Limbless Terrestrial Vertebrates

FOUR main types of locomotion have been described in limbless terrestrial vertebrates^{1,2}. Three of these (serpentine, concertina and sidewinding) depend on lateral undulations which are essentially similar to those of aquatic vertebrates, although more complex. The fourth, rectilinear locomotion, is found in some limbless animals which need to move in conditions which prohibit lateral undulations. The skin in these animals is largely free from the underlying muscles for part or all of the body circumference, being attached only by specially developed cutaneous muscles. These move the skin in segmental units and also transmit the locomotor forces to the body, which is driven forwards continuously while the skin is regionally engaged in static friction with the substrate. The spinal column and ribs remain straight. In amphisbaenids, in which rectilinear locomotion is best developed³, the external appearance resembles that of an earthworm. The skin folds between annular regions of attachment to produce thickened regions which pass along the body.

The limbless amphibians (caecilians, Apoda or Gymnophiona) look even more like earthworms. The skin, musculature and many of the internal organs are segmentally organized. Like amphisbaenids they are able to move by worm-like regional contractions as well as by lateral undulations. The taxonomy of these animals has only recently received detailed attention⁴. Most of the 155 species described seem to be carnivorous burrowing animals, which are distributed throughout the tropics (excepting Australia). They seem especially successful at medium altitudes, where they are usually found in moist, humic soil, often near water. The remaining twenty or so species form an aquatic family (Typhlonectidae) confined to South America.

The mechanisms of movement in caecilians have apparently been ignored since they were thought to lack locomotor specializations¹. A study of *Hypogeophis* has demonstrated that, far from being unspecialized, this amphibian is able to move by a unique method which makes widespread anatomical demands,

Fig. 1 The caecilian *Hypogeophis* moving through a plastic tube. The contracted region A-B is moving backwards relative to the head. Drawn from an X-ray photograph. ($\times 0.5$)



providing an explanation for many of the unique features common to this fossorial group.

Live specimens of *Hypogeophis* collected in the Seychelles were observed while moving in restricted conditions (in a tube or channel) using cine X-ray apparatus. Single X-ray photographs were also taken, of both live and dead specimens, and the behaviour of live animals was observed in laboratory conditions. The skeletal and muscular anatomy of *Hypogeophis* was investigated in the light of the locomotor performance, using dissections and serial sections. H. P. Whiting (personal communication) has observed in an X-ray photograph of a museum specimen of *Ichthyophis* that the spine is folded within the body outline. Published X-ray photographs confirm that this is often the case in fixed specimens of many other genera⁴, and X-ray photographs of *Hypogeophis* show that the same may be true in living caecilians (Fig. 1).

The implications are clear: the shortened, thickened regions visible externally during worm-like movements correspond to spinal flexion, rather than solely to skin contraction as in rectilinear locomotion.

The annuli in the shortened regions grip the sides of the tube or tunnel, providing resistance against which the head is pushed forwards as the spine straightens. The tail region is pulled forwards as new wave-forms are developed, the thickened region containing spinal folds passing rapidly backwards relative to the head. Two such contracted regions may be present at the same time.

The result is very worm-like, the spine replacing the hydrostatic skeleton, but the skin and body-wall muscles performing in much the same way as in worms, and with a similar annular organization. This movement will therefore be termed vermiform locomotion.

This method of locomotion has special advantages to a burrowing animal. As in rectilinear locomotion, lateral flexions of the body are not necessary, which permits movements in tunnels in which most limbless tetrapods would be helpless. Vermiform locomotion has the advantage over rectilinear that more power can be produced, since large regions of the massive spinal musculature are involved rather than merely thin bands of cutaneous muscles. *Hypogeophis* is able to ram through soft earth by vermiform locomotion when unable to "swim" through by lateral undulations. Amphisbaenids probably use rectilinear locomotion chiefly for passing through tunnels previously dug by head movements³.

The evolution of vermiform locomotion was probably accompanied by increased internal stresses caused by the mobile spine and surrounding muscle, and the regional con-

tractions and expansions of the body. The anatomy seems much modified to meet these demands. This will be discussed in detail later, but the essential modifications in muscular arrangement can be clearly seen in transverse sections (Fig. 2).

The segmental body-wall muscles are closely bound to the skin, the myosepta being continuous with the inner dermal connective layers. To move laterally within the body wall, the spinal muscle is free of attachment except at the skull and tail, and by a thin sheet of muscle (m. transversus) and connective fibres running from the mid-line ventro-laterally on each side. This sheet is able to transmit the forces between the skin, engaged with the tunnel wall, and the spinal column. The only other connexions are provided by looped spinal nerves and blood vessels, which are well able to accommodate the movement of the spinal muscle relative to the body wall without risk of rupture.

The ribs are firmly bound to the vertebrae, but they can move in a plane joining the dorsal and ventral articulations. As the spine is pressed laterally against the body-wall muscles the spinal muscle distorts, extending downwards, and the rib on that side is pressed downwards and backwards nearer the spine.

Although the ribs are larger in caecilians than in other living amphibians it is clear that vermiform locomotion could not have developed had the ribs originally extended into the body-wall muscle close to the skin, as in reptiles. Reptiles were thus prevented from developing this locomotory method by their use of the ribs in respiratory movements.

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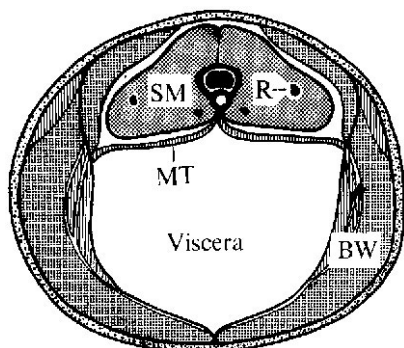


Fig. 2 Diagrammatic transverse section through the mid-body region of *Hypogeophis*. SM, Spinal muscle; R, rib; MT, transversus muscle; BW, body-wall muscles.

Threshold Levels for Damage of the Cornea following Irradiation by a Continuous Wave Carbon Dioxide (10.6 μ m) Laser

CORNEAL damage of varying severity has been studied in the rabbit (*Cuniculus oryctolagus*) and monkey (*Macaca mulatta*) following exposure to a continuous wave carbon dioxide (10.6 μ m) laser. The laser consisted of a 1.5 m glass tube with a water cooled jacket. The tube contained a mixture of carbon dioxide (partial pressure 0.64 mm Hg), nitrogen (partial pressure 1.28 mm Hg) and helium (partial pressure 6.08 mm Hg). A curved stainless steel mirror and an Irtran plain mirror, with a 0.3 cm diameter window, formed a hemispherical cavity. The tube was excited by a 10 kV d.c. supply capable of delivering 100 mA. The mirrors were adjusted to give a TEM₀₀ mode pattern. The emergent beam, which had a divergence of 4 m radians measured between 1/e points, was directed through a limiting aperture of approximately 0.2 cm diameter and finally through an aperture

of 0.25 cm diameter placed directly in front of the eye. The distance between the apertures determined the incident corneal power density. The power distribution of the beam emitted by the laser was Gaussian and beyond the final aperture it was approximately rectangular, that is at a distance of 1 m the edges were limited to 88% of the centre of the Gaussian curve. The total power output of the laser was 20 W.

In each animal an area of about 0.05 cm² (0.25 cm diameter) was irradiated for 70 ms. The exposure was carried out during pentobarbitone sodium anaesthesia (30 mg/kg intravenously).

Three grades of corneal damage were recognized. Grade I, which could be observed but not photographed by slit lamp microscopy, was a very faint opalescence of the epithelium. These lesions resolved within 24 h in the rabbit and within 48 h in the monkey. A grade II lesion involved epithelial loss, which persisted beyond the duration of a grade I lesion, but healed completely within 7 days, and a grade III lesion involved coagulation of the substantia propria with scarring of the cornea.

In ninety-eight pigmented rabbits, weighing between 1.5 and 3.2 kg (mean weight, 2.1 kg), 629 exposures were made with corneal incident power densities ranging from 2.5 to 35.7 W cm⁻². In this species the presence of the precorneal film was ensured by irrigation of the eye with normal saline 45 s before exposure. The 50% probabilities of damage were 5.8 W cm⁻² for grade I, 9.7 W cm⁻² for grade II and 17.4 W cm⁻² for grade III. The lowest power density which led to reversible damage (grade I) was 4.0 W cm⁻² and to irreversible damage (grade III) was 8.0 W cm⁻².

In six monkeys, weighing between 4.0 and 5.2 kg (mean weight, 4.7 kg), eighty-eight exposures were made with corneal incident power densities ranging from 2.0 to 21.0 W cm⁻². Probability analyses were not applicable to this more limited series but the lowest power density which led to reversible damage (grade I) was 6.9 W cm⁻².

Vassiliadis *et al.*¹ reported that the 50% probability of minimal damage in the rabbit was 22.0 W cm⁻² and in their studies the lowest power density which produced damage appeared to be about 21 W cm⁻². We consider that many factors may be responsible for the differences between these and our results. We have used a very faint opalescence as the criterion for minimal (grade I) damage but Vassiliadis *et al.*¹ did not use such a small change in corneal structure as their lesions could be recorded easily by slit lamp photography.

There are also differences in experimental techniques. Vassiliadis *et al.*¹ defined corneal power density as the total power contained in the beam divided by the area contained by the 1/e point of the Gaussian beam distribution, whereas in our studies it was defined as the total power passing through the aperture in front of the cornea divided by the area of the aperture. A difference of 25% in the stated figure for power density could result from identical exposures using these two methods of expressing power density. Further, in their study¹ change in power density was accompanied by change in the area of cornea irradiated and the influence of area irradiated on thresholds for damage has not been established. This is a factor which needs consideration. Their techniques of measurement are not feasible if the irradiated area is to remain constant and the results could suggest, to the unwary, a higher power density than necessary to produce minimal injury. It must also be borne in mind that Vassiliadis *et al.*¹ used an exposure duration of 55 ms and calculations on their data suggest that for an exposure of 70 ms the 50% probability of minimal damage would be reduced to 18.0 W cm⁻².

Although the primate cornea is almost certainly less sensitive to 10.6 μ m irradiation than the rabbit we consider that data obtained from the rabbit should continue to be used for safety considerations in man, at least until more experience is gained. We recommend that the derivation of hazard levels for continuous wave carbon dioxide (10.6 μ m) lasers should now be based, for most purposes, on the lowest power which we have observed to produce minimal corneal damage within

70 ms, that is 4.0 W cm⁻². It must be emphasized that we have observed corneal scarring in 13 rabbits within a power density range from 8.0 to 14.0 W cm⁻².

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¹ Vassiliadis, A., Peppers, N., Dedrick, K., Chang, H., Honey, R. C., Zweng, H. C., Peabody, R. R., Rose, H., and Flocks, M., *Stanford Research Institute Report 6680* (Menlo Park, California, 1968).

Comparative Psychotomimetic Effects of Stereoisomers of Amphetamine

GRIFFITH's demonstration in 1968 that amphetamine psychosis could be induced safely in non-psychotic human subjects made it feasible to study this psychosis in controlled experimental conditions¹, and later the clinical symptoms induced by large doses of amphetamine were identified^{2,3}. There were also attempts to investigate pathogenic factors in this condition, using pharmacological pretreatments which affected biogenic amines, and observing the effects on behavioural responses to amphetamine^{3,4}. Another approach to the study of possible pathogenic factors was suggested by recent reports^{5,6} of differential biochemical and behavioural effects of *d* and *l*-amphetamine. The essence of these findings is that the *d* form of amphetamine was found to be ten times as potent as the *l* form in inhibiting accumulation of noradrenaline in synaptosomes from noradrenergic brain areas, while the two forms were equipotent in their effects on the accumulation of dopamine in synaptosomes from the striatum. Behavioural correlates in rats indicated a similar 10 to 1 potency for *d* against *l*-amphetamine for the induction of motor hyperactivity. The *d* isomer, however, proved only one to two times as potent as the *l* form in inducing stereotyped behaviour in rats. This suggested that the motor activity induced by amphetamine was noradrenergically mediated. The results with regard to stereotypy, however, suggested that dopaminergic, or other non-stereospecific mechanisms, were largely involved in the induction of behavioural stereotypy, but that noradrenergic mechanisms might also contribute since the potency of *d* to *l*-amphetamine was found to be between 1 and 2 to 1, not 1 to 1 as might be expected if only non-stereospecific mechanisms were involved. Moreover, these findings were consistent with biochemical and neuroanatomical studies⁷⁻¹⁰ which suggested a critical role for dopaminergic mechanisms in the induction of behavioural stereotypies.

We therefore reasoned as follows. Psychosis can, of course, only be studied in humans. Snyder's data⁶, however, suggested that the differential behavioural response of subjects to *d* and *l*-amphetamine might provide clues to psychotogenic mechanisms. If noradrenergic mechanisms and behaviourally correlated motor stimulation were critical in psychotogenesis then one might expect *d*-amphetamine to have ten times the potency of the *l* form in inducing psychosis as a behavioural effect. Similarly, if dopaminergic mechanisms only were involved, then one might expect the two compounds to be equipotent in causing a psychosis. If animal stereotypy is a valid model for the stimulant psychoses in humans, then a potency for *d* against *l*-amphetamine of the order of between 1 and 2 to 1 might be anticipated.

We conducted our experiment as described in detail previously³. Basically, it is similar to the methodology developed

by Griffith², but involves somewhat larger individual doses. Amphetamine is administered orally, and 1 h later pulse, blood pressure and temperature are taken. The next dose was determined on the basis of the stability of these signs. The maximum hourly dose used was 50 mg, but smaller doses were administered when effects on pulse, blood pressure and temperature were noted. Amphetamine was administered hourly around the clock with a physician in constant attendance. Behavioural effects were identified by psychiatric interviews every 2 to 3 h. Two interviews each day were videotaped. Racemic amphetamine was given before experiments with the *d* and *l* isomers to establish approximate thresholds for behavioural effects in each subject.

Table 1 Stereoisomeric Form, Cumulative Dose, Duration of Administration and Behavioural Response of Subjects to the Administration of Amphetamine in Large Doses

Patient No.	Type of amphetamine used	Cumulative dose (mg)	Time (h)	Behavioural response (0-6)
1	<i>d, l</i>	540	30.0	4
	<i>d</i>	510	26.25*	4
	<i>l</i>	640	30.0	5
2	<i>d, l</i>	465	22.75	6
	<i>d</i>	270	17.25	5
	<i>l</i>	415	22.50	4
3	<i>d, l</i>	400	24.5	3
	<i>d</i>	475	25.0	3
	<i>l</i>	475	21.25	3

* Tachycardia necessitated discontinuation of experiment.

The stereoisomeric forms of amphetamine, cumulative doses, and the time for which amphetamine was administered are indicated in Table 1; the numbers in the last column refer to the intensity of the psychosis induced, scored from 0 to 6. The qualitative aspects of these responses will be described in detail later.

The intensity of symptomatology and dose-response relationships do not support the idea that noradrenergic mechanisms are critical in precipitating amphetamine psychosis. Certainly, the psychotogenic potency was nowhere of the order of 10 to 1 for the *d* against the *l* isomer. If just the *d* and *l* experiments are considered, subject 1 showed approximately the same degree of symptomatology at doses of 510 and 640 mg of *d* and *l*-amphetamine, respectively. Subject 2 showed slightly more severe symptoms after 270 mg of *d*-amphetamine than after 415 mg of the *l* isomer, while the third subject showed a similar behavioural response after the same dose of the *d* and *l* isomers. In other words, the mean dose of *d*-amphetamine given to these three subjects was 418 mg and that of the *l* isomer was 510 mg—both induced comparable syndromes in the three subjects and equal mean scores of behavioural disturbance of 5 (on a scale of 0-6). This suggests that noradrenergic mechanisms are not the most critically important factor in amphetamine psychosis, and further studies should be focused on the role of dopaminergic or other non-stereospecific mechanisms. Moreover, the fact that dose-response relationships indicate a psychotogenic potency for the *d* and *l* isomers of amphetamine of the order of between 1 and 2 to 1 suggests that animal stereotypy, in which dose-response relationships are of the same order^{5,6,11}, should be utilized as an animal model for the human stimulant psychoses. The established role of dopaminergic mechanisms in the induction of these behavioural stereotypies⁷⁻⁹ suggests that the role of these mechanisms in the pathogenesis of the human stimulant psychoses should be investigated. Further support for this orientation comes from the observation of psychotic symptoms in Parkinsonian patients receiving L-dopa¹² (which increases brain dopamine more consistently than nor-

adrenaline¹³), and from the demonstrated capacity for L-dopa to induce stereotypy in rats¹⁴, cats¹⁵ and dogs¹⁰.

The striking clinical similarity of amphetamine psychosis to paranoid schizophrenia¹⁶, moreover, suggests that these conditions might have common mechanisms. The fact that drugs which antagonize amphetamine stereotypy in animals also tend both to be useful neuroleptics in the treatment of schizophrenia and, in addition, cause a Parkinsonian syndrome in humans also suggests that subsequent investigators focus on the role of dopaminergic mechanisms in naturally occurring psychoses—especially those in which paranoid symptoms are prominent.

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Reaction of Metallic Copper with Biological Substrates

It has been shown by Zipper *et al.*¹ that a plastic T-shaped intrauterine device is much more effective in preventing pregnancies in women if its stem is encased by copper wire. After removal of the copper intrauterine device from the human uterus, the copper wire is blackish and weighs less than at the time of insertion; a device with a 200 cm² copper surface loses 60 µg per day of usage (personal communication from H. J. Tatum).

This loss of metallic copper has prompted me to investigate the interaction of metallic copper with various biological substrates. In all experiments electrolytic grade copper foil of various dimensions was placed in solutions of substrates incubated at 37.5° C. After various times of incubation the solutions were analysed for cupric ions with the diethyl ammonium salt of diethyl dithiocarbamic acid, which forms a yellow chelate with cupric ions.

A copper strip with a surface area of 400 mm² was placed in a mixture of approximately 0.5 ml. of human uterine secretion and 2 ml. of physiological saline (0.9%). The uterine

secretion was initially a thick clear mucoid material. After 18 h of incubation this material was lysed, and no longer viscous; a precipitate had formed and the copper strip was blackened. The Cu^{2+} concentration in the solution was 1.8×10^{-3} M. An 18 h incubation of a copper strip in 2.5 ml. of saline solution alone yielded a Cu^{2+} concentration of 4×10^{-5} M. Because uterine secretions are slightly alkaline, a copper strip was incubated for 18 h in pH 8 carbonate buffer, but the corrosive action was slight as with saline. Uterine secretion incubated with saline but without the metallic copper still showed a coherent mucoid mass after 18 h of incubation. The amount of copper dissolved by the uterine secretion, calculated for a 200 mm^2 Cu surface, amounts to $60 \mu\text{g}$ per day, if one assumes 1 ml. of secretions per day, agreeing well with the clinical data.

An 18 h incubation of 1.8 ml. of human ovulatory cervical mucus (without added saline) with a copper strip (400 mm^2 total surface) showed a lysis of the mucoid material and a Cu^{2+} concentration of 1.0×10^{-2} M. The copper-incubated cervical mucus was brought into contact with washed sperm, which was inactivated within 2 h of incubation at 37.5°C ; in a parallel experiment with normal cervical mucus there was no comparable inactivation.

To elucidate the mechanism of the dissolution of metallic copper, bovine serum albumin was used as a model substrate, since the interaction of serum albumin and mucins gives cervical mucus its cohesiveness. Bovine serum albumin dissolved in water showed a dissolution of metallic copper which was proportional to the time of incubation (measured up to 24 h) and to the surface area of the copper strip ($80\text{--}720 \text{ mm}^2$). Fig. 1 shows that the rate of dissolution of copper increases both with increasing salt and serum albumin concentrations. During this dissolution process protein is precipitated. The turbidity as a function of albumin concentration (Fig. 2) had a pronounced maximum.

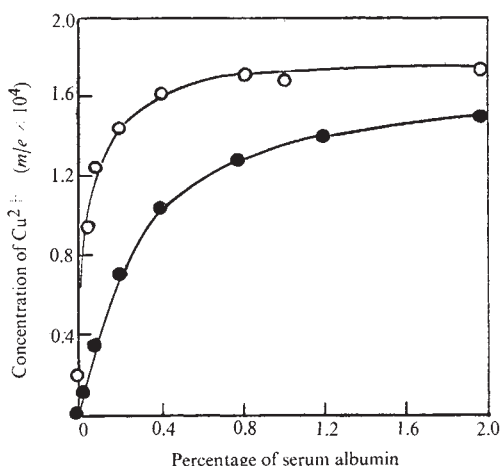


Fig. 1 Cupric ion concentration in serum albumin solution after 90 min incubation of 400 mm^2 copper strip in 5 ml. of protein solution. ○, Albumin in 0.9% NaCl; ●, albumin in water.

It was noticed that the portion of a copper strip immersed in albumin solution became dull due to precipitated protein on its surface, the portion of the strip extending into the air remained shiny, but a thin line of the air-albumin solution interface became black. Oxygen seems to play a role in the copper dissolution process.

When oxidized and reduced glutathione (1×10^{-2} M) was incubated with copper strips, the former caused the formation of cupric ions whereas the latter showed only a slight reaction. These observations indicate that the disulphide bond is a critical group in the copper dissolution process by biological materials, presumably acting as an oxidizing agent in the

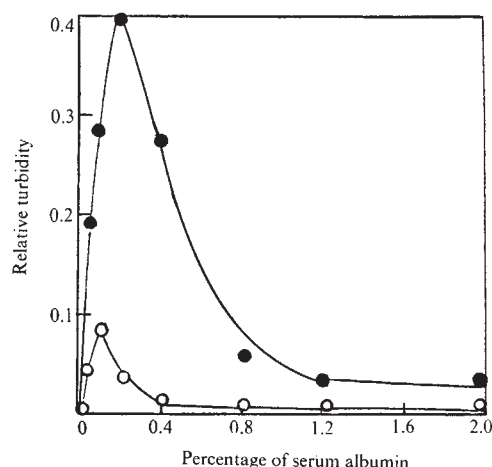


Fig. 2 Relative turbidity (absorbance at 500 nm for 1 cm path length) of copper-incubated albumin solutions. Conditions as in Fig. 1.

oxidation of metallic copper to cupric ion. The reduction potential of glutathione is -0.35 V and the potential for the process $\text{Cu} \rightarrow \text{Cu}^{2+} + 2\text{e}$ is -0.337 V . The oxidation of copper by the disulphide bond is not more easily accomplished if the first step $\text{Cu} \rightarrow \text{Cu}^+ + \text{e}$ (-0.521 V) is followed by the subsequent oxidation of cuprous to cupric ion by oxygen.

The precipitated protein illustrated in Fig. 2 is albumin with some S-S bonds broken. A saline-free 0.2% albumin solution without metallic copper but containing 7×10^{-5} M CuSO_4 did not precipitate after 90 min of incubation (compare with Figs. 1 and 2). The sharp maximum in turbidity arises from the precipitation of the modified albumin by cupric ions which can be reversed at high albumin concentration. If fresh albumin is added to a precipitated albumin solution which has been treated with metallic copper, the precipitate slowly disappears. Apparently, once cupric ions are formed, there is competition for these ions by both modified and normal albumin; the latter is well known to bind cupric ions although it is not precipitated at these low Cu^{2+} concentrations.

Other proteins which dissolve metallic copper include ovalbumin, insulin, alkaline phosphatase and carbonic anhydrase. The two enzymes lose their activity after incubation with metallic copper when a Cu^{2+} concentration of 7.5×10^{-5} M is reached. On the other hand, incubation without the metal but with 7.5×10^{-5} M CuSO_4 does not appreciably lower enzyme activity. This again indicates a modification of the proteins at the metal surface, rather than an action of cupric ions.

The finding that disulphide bonds oxidize metallic copper suggests a number of ways by which the copper intrauterine device might act. It may precipitate albumins and change the uterine wall in such a way as to prevent implantation; it may reduce stickiness of the uterine secretions and suppress implantation; it may lyse the mucoid materials which may then no longer provide a supporting medium for transport of spermatozoa; finally, crucial enzymes may be inactivated by the metal and cupric ions may kill sperm. Thus the reaction of biological substrates at a metallic copper surface results not only in the formation of cupric ions, but also in a drastic transformation of the physical and chemical characteristics of disulphide-containing biopolymers.

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Incidence of R⁺ *Escherichia coli* in Coastal Bathing Waters of Britain

Escherichia coli able to transmit antibiotic resistance to pathogenic organisms has been found in British rivers, their principal source being insufficiently treated human sewage¹. As sewage contamination is considered to be fairly widespread in coastal bathing waters in Britain², I have looked for these *E. coli* here.

of faecal origin, to determine their antibiotic resistance pattern and to discover if their resistance was transmissible.

The results of examining ten samples of seawater collected on the same occasion from each of fifteen bathing beaches are summarized in Table 1. There was great variation in the concentration of antibiotic-resistant coliform organisms in samples from the different beaches. For example, relatively large numbers were isolated from all ten samples collected at Penarth, whereas none were isolated from the ten collected at Brighton. From some beaches, such as Whitstable, only

Table 1 Concentration of Antibiotic-resistant Coliform Organisms in Seawater from Bathing Beaches

Beach	Viable coliform organisms per 20 ml. * resistant to antibiotic					Total
	C	T	S	N	A	
Penarth	5 (3-15)	50 (20-80)	50 (20-100)	4 (2-15)	500 (200-1,000)	4,000 (1,600-8,000)
Herne Bay	4 (1-16)	30 (20-70)	10 (2-40)	10 (0-2)	20 (3-40)	2,000 (250-8,000)
Sheerness	1 (1-5)	20 (10-30)	35 (20-40)	1 (0-1)	40 (30-60)	900 (400-1,600)
Ogmore	1 (0-4)	8 (3-30)	10 (2-40)	0 (0-1)	20 (5-70)	600 (200-800)
Clacton	1 (0-3)	10 (6-20)	9 (3-10)	2 (0-5)	5 (1-10)	300 (100-400)
Barry Island	1 (0-2)	7 (2-20)	10 (5-15)	0 (0-2)	45 (30-80)	400 (300-600)
Ramsgate	0 (0-1)	4 (1-8)	2 (1-4)	0 (0-3)	3 (1-15)	100 (50-250)
Whitstable	0 (0-4)	2 (1-30)	2 (1-20)	0 (0-4)	4 (0-20)	250 (50-2,000)
Canvey Island	1 (0-4)	3 (1-7)	1 (0-2)	0 (0-1)	30 (8-30)	200 (50-400)
Broadstairs	0 (0-3)	3 (1-8)	3 (0-6)	0 (0-1)	5 (3-10)	150 (50-800)
Lowestoft	0 (0-1)	2 (0-4)	2 (0-3)	0 (0-0)	1 (0-5)	100 (20-400)
Yarmouth	0 (0-1)	2 (0-3)	2 (0-3)	0 (0-0)	3 (1-8)	200 (100-400)
Eastbourne	0 (0-0)	0 (0-2)	0 (0-8)	0 (0-2)	0 (0-3)	10 (0-30)
Margate	0 (0-0)	0 (0-3)	0 (0-0)	0 (0-0)	0 (0-20)	6 (0-40)
Brighton	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1 (0-3)

C, Chloramphenicol; T, tetracyclines; S, streptomycin; N, neomycin; A, ampicillin.

* Median count followed by, in parentheses, the range of counts for ten samples collected on the same occasion from different sites on the beach.

Samples of seawater (250 ml.) were collected in sterile glass containers, usually from both ends of each beach and at eight approximately equidistant intermediate sites. They were collected a few metres from the shore at high water because this is the most common time for bathing, although while the survey was performed (spring 1971) the beaches were rarely used for this purpose. The beaches were randomly chosen for sampling in that no information had been sought on the disposal of sewage in their vicinity.

The numbers of viable antibiotic-resistant and sensitive coliform organisms in the samples of seawater were estimated by the method previously used to examine river water¹, except that the Petri plates of MacConkey's agar containing different antibiotics were each inoculated with the centrifuged deposit of 20 ml. of each sample instead of 1 ml. of each sample. The methods used in the river water studies were also used to identify coliform organisms as *Escherichia coli*

one or two samples contained high concentrations of antibiotic-resistant coliform organisms.

The results of examining seawater from the same ten sites on Southend beach, some 7 km long, on seven occasions, 14-21 days apart, differed greatly (Table 2). For example, very few coliform organisms, resistant or sensitive, were isolated from any of the ten samples collected on the first occasion whereas relatively high concentrations were found in those collected on the fifth occasion, a day when the sea was unusually turbulent and there was a strong onshore wind. On four occasions, considerably higher numbers of coliform organisms were isolated from water from one or two sites than from the water from the other sites, but the particular sites involved were not the same on each occasion.

In general, the ratio of the concentrations of the different kinds of antibiotic-resistant coliform organisms to each other and to the antibiotic-sensitive organisms in the seawater

resembled that in human sewage¹. Three specimens, however, contained unusually high proportions of coliform organisms possessing the same antibiotic-resistance pattern; one of these contained 2,000 coliform organisms in 20 ml., more than 75% of which were resistant to neomycin, streptomycin and sulphonamides.

The Eijkman test was done on a representative collection of strains of coliform organisms isolated from all bathing waters examined. On the basis of this test, seventy-eight of eighty-three strains isolated because they were chloramphenicol-resistant were classified as faecal type *E. coli*. The corresponding figures for tetracycline-resistant strains were 107 of 111, for streptomycin-resistant strains were sixty-eight of ninety-four, for neomycin-resistant strains were forty-two of forty-five, for ampicillin-resistant strains were fifty-two of 100 and for fully antibiotic-sensitive strains were seventy-four of 138.

contamination with human sewage, particularly when the composition of the coliform population resembles that in human sewage, as mentioned before. On this basis, some of the bathing waters examined seemed to be relatively heavily contaminated throughout their length, or in localized regions only, and others did not. The great variations between the results of the examinations of Southend seawater collected on different occasions clearly indicated, however, that freedom from contamination cannot be determined from the result of one set of examinations only. The heaviest degree of contamination at Southend was found on the occasion when the sea was most turbulent due to a strong on-shore wind, supporting the view that such conditions may favour beach pollution². A sample of seawater in which *E. coli* of one particular antibiotic resistance pattern comprised practically the whole of its coliform content can only be explained by assuming that the

Table 2 Concentration of Antibiotic-resistant Coliform Organisms in Seawater on Different Occasions from Southend Beach

Occasion	Viable coliform organisms per 20 ml. * resistant to antibiotic					Total
	C	T	S	N	A	
1	0 (0-0)	1 (0-4)	1 (0-4)	0 (0-1)	5 (0-10)	30 (5-60)
2	0 (0-0)	0 (0-30)	0 (0-4)	0 (0-0)	2 (0-40)	20 (10-100)
3	1 (0-3)	3 (0-30)	4 (0-20)	0 (0-6)	70 (0-200)	200 (40-1,000)
4	0 (0-5)	2 (0-60)	1 (0-50)	1 (0-3)	10 (0-40)	50 (50-300)
5	3 (0-15)	25 (10-150)	25 (3-2,000)	3 (1-2,000)	100 (20-2,000)	1,200 (400-8,000)
6	1 (0-6)	15 (1-40)	10 (0-20)	0 (0-2)	30 (0-100)	600 (400-2,000)
7	0 (0-3)	4 (0-200)	1 (0-20)	0 (0-0)	7 (0-60)	150 (40-4,000)

*For other details see Table 1.

Most of the antibiotic-resistant coliforms were resistant to more than one antibiotic. Some were resistant to five or six; this was particularly so in the case of those isolated because they were resistant to chloramphenicol or neomycin.

Forty-six of fifty-four strains of coliform organisms isolated because they were chloramphenicol-resistant transmitted their resistance to *E. coli* K12F⁻ in mixed culture. The corresponding figures for tetracycline-resistant strains were fifty-six of seventy-seven, for streptomycin-resistant strains were thirty-six of seventy-seven, for neomycin-resistant strains were thirty-three of thirty-six and for ampicillin-resistant strains were twenty-five of seventy-six. Of twenty multiply resistant strains isolated from different samples of seawater on account of their chloramphenicol resistance, eighteen transmitted their resistance to *Salmonella typhi*.

Broth cultures of five strains of faecal *E. coli*, possessing different antibiotic resistance patterns and isolated initially from bathing waters, were added to different samples of seawater in amounts sufficient to give a final concentration of 10,000 viable organisms per ml. The samples were then kept at room temperature. After 1 day, the concentration of the resistant organisms in the samples had decreased by 0-60%. After 2, 3 and 4 days, the corresponding percentages were 25-80, 50-100 and 97-100 respectively. No resistant organisms were found in any of them after 5 days.

Some coliform organisms found in seawater and identified by biochemical tests as faecal type *E. coli* might have originated in marine life or wild birds. The presence of R⁺ forms of such organisms in seawater provides stronger evidence of

sample contained a particle of faeces from an individual who had recently been treated with an antibiotic.

It is a reasonable assumption that bathing waters contaminated to the extent of some in our survey may play a part in the dissemination of R⁺ *E. coli* in the human community. They may also play a part in the dissemination of pathogenic organisms. The lack of incriminating evidence cannot be accepted as proof that they are of little importance in this respect. As far as the R⁺ *E. coli* are concerned, the laboratory studies showed that they did not live for long in seawater, indicating that the sea is a temporary reservoir only of these organisms. Consequently, the present undesirable situation could be corrected immediately if proper disposal of sewage from seaside towns were practised.

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¹ Smith, H. W., *Nature*, **228**, 1286 (1970).

² Report, *J. Hyg. Camb.*, **57**, 435 (1959).

Illusions in Perspective

DR HUMPHREY speculates on the thought processes of the Sung school and Italian primitive painters¹. I, too, was puzzled by distortions in the tenth century "Midsummer Rest under a Locust Tree" and in Ugolino's "Resurrection".

If you apply a ruler to the graphic illustrations in Dr Humphrey's paper, it seems that the back edge of the philosopher's couch in Fig. 5 is in fact some 2 mm longer than the front; the corresponding inside dimensions of the lid of Christ's sarcophagus in the photograph in Fig. 6 differ by about 1.5 mm. Whatever the artists thought they were up to, they should not be accused of confusing their trapezoids with what Dr Humphrey perceives as a "perfect parallelogram". Not that I wish to question his explanation of the artists' distortions in terms of "mediaeval practice to prefer a formal rule to the mundane evidence of the senses".

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¹ Humphrey, N. K., *Nature*, **232**, 91 (1971).

Contrast Illusions in Perspective

THERE seems to be some confusion in Humphrey's account of "Contrast Illusions in Perspective"¹. This may be due to over-compression, especially of a crucial paragraph (page 92, para. 3), which contains: "The nature of the optical projection to the eye is such that more distant objects on the whole give rise to smaller retinal images than near ones, and distance is therefore a guide to retinal size. The expected size of the further of two objects is less than that of the nearer, and hence if we see two lines which appear to be different distances but have the same actual length, we judge the further to be longer than the nearer". There are some curious features in this which though perhaps obvious should be spelled out, to avoid an already confused situation being worse confounded. (1) It is clearly not retinal image size which Humphrey supposes is "guided" by distance. Image size is given directly, by the geometry of object size and distance and the optical characteristics of the eye. The intended meaning must surely be along the lines of "perceived size"; but this is a very different matter from retinal image size—hence, indeed, the problem. (2) It is not the expected size of objects, lying at various distances, which is the issue but the image size corresponding to various object distances. (This is given directly by object size and distance, as stated.) (3) Perceived size (assuming this is what is meant, in place of "retinal size") cannot be given by distance *per se*. It would have to be given (or "guided") by available information of distance. This could be real-time sensory data; or it could be stored information, as of the shapes of familiar objects, such as tables.

It is a matter for experiment to discover the kinds of sensory data used for giving perceived size and distance. We know that perspective convergence of parallel lines and texture gradients are important; especially so for vision with a single fixed eye, as in viewing pictures. We know less about which object shapes are assumed for inferring size or distance from familiar objects; but we know this does occur, for example, from experiments with depth-ambiguous wire figures which change apparent shape as perception changes, though the retinal image (real-time sensory data) remains constant².

(4) Again we cannot suppose that signalled distance is a guide to retinal image size. Image size is given directly from the geometry of the situation (as stated in (1) above) and so cannot be "guided" by distance *per se* or by available (real-

time or stored) information of distance. If, however, Humphrey does mean by "retinal size" something like "perceived size" or "apparent size", then he is saying that signalled or assumed distance affects perceived size. This is certainly so: it follows from the classical Emmert's law demonstration, from depth-ambiguous wire figures which change their shape with depth reversals² and many other demonstrations. But it is perceived size and not retinal size which changes as a function of signalled or apparent distance. To confuse the two is to wreak havoc with any discussion of these problems.

(5) Although for the normal world of objects sensory information and assumed distance affect perceived size, the case of line pictures is complicated by the fact that they are seen both as flat patterns of lines on a flat background which they physically are, and as depicted objects, in a different space, which they represent. The distortions evidently follow the depicted distances, rather than the physical distances which indeed are absent for a physically flat picture. Several implications follow. An account of the phenomena simply in terms of retinal patterns and directly associated physiological activity can hardly be adequate, for it is the significance of the patterns in terms of familiar objects, especially their usual shapes, which are determining apparent size. (This takes us to concepts like "software" computer concepts. Accounts in purely physiological terms seem inadequate, for they cannot handle significance or probabilities of object characteristics. Hence the need for "cognitive" concepts in perceptual theory. Cognitive processes will, however, be mediated by physiological processes—as computer hardware mediates the "software" mathematical and logical processes of a computer. Given the physiological/cognitive distinction, errors of size might be attributed to errors in physiological processes, mediating cognitive "programmes", or inappropriateness of the programmes themselves.

By invoking "expectancy" Humphrey is calling on a cognitive concept. I would agree that this is appropriate for the rectilinear projection distortions, though not for the "waterfall" after-effect of motion, in which object recognition is not involved. (The induced motion of the "waterfall effect" does not, as an after-effect of retinal image motion, depend on object recognition, either for inducing it or observing it.)

There is something odd, at least at first sight, about explaining something unexpected (the queer shapes of tables drawn in rectilinear projection) in terms of expectation. How can expectation give unexpectedness? I think it can, but the argument requires another and vital step. We may plausibly suppose that the usual perceptual scaling constants are applied to rectilinear projections of objects, much as though the depicted objects were seen with the normal perspective of retinal images when viewing the objects directly. Image size normally shrinks with increased object distance (giving retinal perspective), and this is normally compensated (giving size constancy), so we should expect depicted distance to be associated with expansion, in these zero-perspective pictures—if normally appropriate size scaling is evoked by the "recognition" of the picture as depicting an object, such as a table. Humphrey correctly points out that the distortions increase as the pictures are drawn more lifelike, apart from the absence of perspective. The more strongly it is recognized as a table, the greater the distortion. We may, I believe, describe the distortions by saying that the usual perceptual size corrections for compensating image shrinking with object distance are operating, according to the depicted objects, but that this is inappropriate for these pictures because there is no perspective to compensate³. Features depicted as more distant are perceptually expanded. They are expanded by the size scaling, itself established by many experiments, which normally compensates retinal perspective shrinking, to give size constancy in the three dimensional world of normal objects. In rectilinear projections there is no perspective shrinking with depicted distance: so the normally appropriate corrective scaling is inappropriate—and so generates the observed

distortions. Is there any reason not to believe in this account of the matter?

Finally, to say that "expectancy" and "contrast" are concepts applicable to illusions ranging from colour changes after wearing red glasses, the "waterfall-effect" of induced movement, the "size-weight" illusion, after-effects of size, as well as the rectilinear projection illusions and presumably also perspective illusions, is either to have a deep insight into the mechanisms of perception or to give such a low resolution description that important differences between them are blurred.

A vital distinction which should not be lost is between (a) neural systems becoming modified, or adapted, by maintained or unusual stimulation ("physiological adaptation"), or by prolonged or unusual sensed object-characteristics ("cognitive adaptation") and (b) normally functioning physiological or cognitive processes, being applied inappropriately in the given situation. Inappropriateness can generate errors and distortions in unusual situations though the system is functioning normally; but to recognize that this is the case we must understand the significance of the physiological and cognitive processes, and discover why they are inappropriately applied, and in what ways they are inappropriate, in the illusion situation. This involves looking at each illusion situation very carefully: facile generalizations prevent our seeing the significance of the phenomena in terms of normal but misapplied, or abnormal, functioning of the perceptual system. Perhaps a theoretical classification is needed here; the following seems useful: (A) physiological illusions, generated by physiological (1) adaptation, (2) inadequacy, (3) inappropriateness; (B) cognitive illusions, generated by cognitive: (1) adaptation, (2) inadequacy, (3) inappropriateness. Although there is much room for debate and further knowledge, all illusions can, I submit, be classified with these headings without doing damage to distinctions we need to bear in mind to understand perceptual effects and use the phenomena as tools for understanding perception.

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¹ Humphrey, N. K., *Nature*, **232**, 91 (1971).

² Gregory, R. L., *The Intelligent Eye* (Weidenfeld and Nicolson, London and New York, 1971).

³ Gregory, R. L., *Nature*, **199**, 678 (1963).

Model for a Two-adversary Arms Race

A MATHEMATICAL model for a two-adversary arms race which comprises three features, (i) response to adversary's stockpile, (ii) response to his growth rate and (iii) finite resource limitation, can be described by the pair of equations

$$u_1' = (K_1 u_2 + L_1 u_1') (a - u_1) \quad (1)$$

$$u_2' = (K_2 u_1 + L_2 u_2') (b - u_2) \quad (2)$$

where u_1 and u_2 are the arms stockpile for the two sides; the primed functions, their time derivatives; and a and b , the finite limits to the resources of each. The factors $(a - u_1)$ and $(b - u_2)$ have been used before¹ to describe logistic growth laws, but make the above two equations non-linear.

In this model the responsive coefficients are non-negative constants. If both u_1 and u_1' are positive, so must u_2' . Should

one's stockpile be kept stationary ($u_1' = 0$), the foe's will still grow ($u_2' > 0$) by the second equation. A slight decrease in one's stockpile (u_1' negative but small) will not prevent the foe's growth (u_2' positive by equation (2)) which, in turn, induces a renewed growth in one's stockpile (by equation (1)). Slight rates of disarmament by either side, or both, is not a stable condition. There is an ineluctable return to competitive growth.

There is a critical rate for one's own arms reduction rate, when $K_2 u_1 + L_2 u_1' = 0$, which induces the foe to keep his stockpile level constant. From this critical condition one's stockpile has an exponential decay with relaxation time L_2/K_2 . Disarming slower than this leads to the above mentioned instability; more rapidly, to the foe's disarming. However, one's disarmament rate must be even more drastic than this to attain stable bilateral disarmament. For, if the adversary's induced disarmament rate is slight, one's own rearmament will be induced. That condition is

$$u_1' < -K_2 u_1/L_2 - K_1 u_2/L_1 L_2$$

From this, the greater is each stockpile the greater the response to these, and the less the response to the rate of reduction, the more drastic must one's disarmament rate be to induce the foe to disarm rapidly enough to, in turn, assure oneself. By interchanging subscripts the foe's condition is obtained. The solution of these two simultaneous inequalities has two exponential decay terms. For simplicity, if $K_1 = K_2 = K$ and $L_1 = L_2 = L$, these are $\exp -K(1 \pm 1/L)t/L$. The term with the upper sign is the faster and proper decay.

If bilateral disarmament does not obtain, the ensuing arms race can be examined. In the light of the high priority given to a nation's military capability it is reasonable and certainly convenient to neglect the factors $(a - u_1)$ and $(b - u_2)$ in the first equations. These can then be restated as two second order equations

$$(1 - L_1 L_2) u_1'' - (K_1 L_2 + K_2 L_1) u_1' - K_1 K_2 u_1 = 0$$

and, *mutatis mutandis*, the same for u_2 . Note that the constant coefficients are identical for u_1 and u_2 . If the first coefficient were negative, it would not be possible to have u_1 , u_1' , and u_1'' all positive or all negative. Since there is no obvious self-correction of this sort in an arms race, $L_1 L_2$ cannot exceed unity.

For the special case $L_1 = L_2 = 0$, there is an exponential growth with argument $(K_1 K_2)^{1/2} t$, and the familiar Lanchester N-square law²

$$u_1^2/K_1 = u_2^2/K_2 + \text{constant}$$

When $K_1 = K_2 = 0$, it follows that $L_1 L_2 = 1$. The two-terms solution of the second order equations is particularly simple if corresponding responsive coefficients are identical, so the subscripts may be omitted.

$$u_1(t) = \frac{1}{2}(u_1(0) \pm u_2(0)) \exp \pm Kt/(1 \mp L)$$

Similarly, for $u_2(t)$. The adversary with the initially smaller stockpile will grow faster until both sides have identical increasing capabilities (provided the finite-resource constraint is not imposed). The growth term increases explosively as L approaches unity. In this model greater response to rate of growth corresponds to more rapid escalation.

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¹ Blumberg, A., *J. Theoret. Biol.*, **21**, 42 (1968).

² Saaty, T. L., *Mathematical Models of Arms Control and Disarmament* (Wiley, New York, 1968).

BOOK REVIEWS

Science and Synthesis

Interpretations of Life and Mind. Edited by Majorie Grene. Pp. xvi+152. (Routledge and Kegan Paul: London, October 1971.) £2.25.

CAN anything change the headlong course of history towards greater disasters? The doctrines and religions of the past have failed to promote peace and goodwill. For some the only hope lies in the emergence of a scientific and philosophical synthesis providing not only a better image of man but a compelling vision of what mankind must achieve in this century. This major humanist aim lies behind the title of this volume. In 1965 UNESCO summoned an international colloquium of some forty scholars in memory of two world figures who died in April 1955 and provide symbols of the unifying imagination seeking to construct respectively a scientific/mathematical and a philosophical/ethical cosmology. This report, a late translation from the French edition of 1967, contributes little to the major aim, but contains much of interest on physics.

The main themes covered are Einstein and the scientific synthesis, debates on science and synthesis, and Teilhard de Chardin. The papers on the first two, with one important exception, deal principally with cosmological myths and theories, advanced physical theory, and Einstein's thought. Two call for mention: first, J. R. Oppenheimer's perceptive note on Einstein and the three traditional elements which deeply influenced him—the statistical mechanical interpretation of thermodynamics, the concept of the field, and the principle of sufficient reason—and second, a most interesting twenty-five page study by G. Holton, using unpublished letters, of the relation of Einstein's changing philosophy of physics to Mach's positivism.

Most of the special topics discussed are old, but it is useful to have the fairly recent views of W. Heisenberg, L. de Broglie, and others on the unified field theory, from plurality to unity, determinism and indeterminism, and the organization of scientific research.

The final section on de Chardin expresses appreciation of his personality, his work on palaeontology, and his philosophical and religious doctrine. Scientists should be tolerant of speculative visions, for history shows that they can prove fertile and we are in need of unifying principles. However, in the preface to his *Phenomenon of Man*, de Chardin, surely unwisely, said that this book "must be read purely and

simply as a scientific treatise". Why, then, do his supporters here fail to make a critical analysis of his ideas and to set them in their historical context since several influential thinkers—Bergson, Whitehead, Smuts, and Sir Julian Huxley *inter alia*—have expressed similar views?

The exception referred to is a humanist manifesto by Huxley, who alone examines the perils ahead and how science and synthesis might help. Huxley is strong on diagnosis, but weak on therapy, like nearly all as yet. He identifies, correctly I suggest, four current insanities: military reliance on the H-bomb, economic on the profit motive, political on competitive power units, and biological on unrestricted human reproduction. When Huxley concluded, did those in agreement stand up to be counted, as a tiny nucleus of a future world consensus of the sane? Will UNESCO respond to his plea and continue the debate on the "new organized system of thought and belief (which) is the greatest task of this generation"?

A weakness of this volume is that biological synthesis is not discussed and molecular biology barely mentioned. Was not the Crick/Watson discovery of 1953 an authentic synthesis, perhaps as fertile in its own way as Einstein's metrical tensor law of 1916? This and other limitations are inevitable. So vast a theme could not be covered in this slim volume, for which we must be grateful; parts of it are excellent.

LANCELOT LAW WHYTE

Evolution of Physics

Bergson and the Evolution of Physics. Edited and translated by P. A. Y. Gunter. Pp. xi+348. (University of Tennessee: Knoxville, 1969.) \$10.50.

In the introduction to this collection of essays Professor Gunter presents first a short history of Bergson's life. In spite of the immense success which followed the publication of *L'Evolution Créatrice* in 1907 (Bergson was then forty-eight years old), dark elements were not lacking in his life. The great vogue lasted only a few years, till the First World War. Then his writings were attacked with increasing violence. His influence declined and at the moment of his death in 1941, after years of illness, his way of thinking was already associated in the mind of many people with an aura of mysticism and anti-intellectualism. Even today it is often fashionable to present a few derogatory remarks about his philosophy (ref. 1 provides a recent example). Therefore

the book edited by Gunter is most timely. It contains four parts: quantum physics (contributions by Louis de Broglie, Satoru Watanabé, Olivier Costa de Beauregard, Robert Blanché), relativity (Henri Bergson, Albert Einstein and Henri Piéron, André Metz and Henri Bergson, Günther Plug, J. F. Busch, W. Berteval, Olivier Costa de Beauregard), Bergson and Zeno's paradoxes (Vere C. Chappell, David A. Sipfle) and a concluding summary by Malič Čapek. Most of these articles appeared originally in French or German and have been translated for this book. Except in the section on relativity there are no original texts by Bergson.

"We interpret the past through the present." This saying is well illustrated by Louis de Broglie's article who, in his words, has "been struck by the analogy between certain new concepts of contemporary physics and certain brilliant intuitions of the philosophy of duration". The section on relativity, while it is the longest, is unfortunately the least interesting. As is well known, Bergson's specific method in metaphysics is based on what he called "intuition" and according to his words: "penser intuitivement est penser en durée"². He felt therefore that relativity with its spatialization of time was a threat to his views. Today it may be safely stated that time is no more and no less spatialized in relativistic physics than it is in pre-relativistic physics. It is as meaningful to speak of irreversibility and increase of entropy as it was before. Bergson's struggle with the Lorentz transformation in "Durée et Simultanéité" is as pathetic as it completely misses the point. In his article "The Principle of Relativity and the Spatialization of Time" de Beauregard comes closer to the issue when he notes that "Einstein's great discovery and Bergson's just claims may be less incompatible than they appear at first glance". Indeed in a recent paper Balescu and Brenig³, using the recent developments in statistical mechanics, were able to prove that all relaxation times are invariants in respect to the Lorentz transformations.

Analysing the *durée*, Bergson reached the conclusion that time had to have attributes quite foreign to classical dynamics: "Plus profondément nous pénétrons l'analyse de la nature du temps, mieux nous comprenons que durée signifie invention, création de formes, élaboration continue de ce qui est absolument neuf"⁴. It is indeed quite remarkable how close these views are from those reached in thermodynamics of irreversible processes (see especially refs. 5 and 6).

At the third meeting of the Institut de la Vie, devoted to theoretical physics and biology (Versailles, June 1971), Szent-Györgyi made the following chairman's remarks (preprint): "... We all studied one or another part of living systems. The smaller the unit, the more pure physics and chemistry, but also the less 'alive' it is. ..."

It is fascinating to compare this text with the following one by Bergson (*L'Evolution Créatrice*, page 31, oeuvres page 521): "... Ainsi la 'vitalité' est tangente en n'importe quel point aux forces physiques et chimiques; mais ces points ne sont, en somme, que les vues d'un esprit qui imagine des arrêts à tels ou tels moments du mouvement générateur de la courbe. En réalité, la vie n'est pas plus faite d'éléments physico-chimiques qu'une courbe n'est composée de lignes droites."

It seems to me a weakness of this otherwise very valuable book that these important aspects have been neglected.

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¹ Monod, J., *Le Hasard et la Nécessité* (ed. Le Seuil, Paris, 1970).

² Bergson, H., *La Pensée et le Mouvant*, 30; (Oeuvres, ed. du Centenaire, Presses Universitaires de France, Paris, 1963).

³ Balescu, R., and Brenig, L., *Physica*, **54**, 504 (1971).

⁴ Bergson, H., *L'Evolution Créatrice*, 11 (Oeuvres, 503).

⁵ Glansdorff, P., and Prigogine, I., *Structure, Stability and Fluctuations* (Wiley Interscience, New York, 1971); (French edition by Masson, Paris, 1971).

⁶ Eigen, M., "Self-organization of Matter and the Evolution of Biological Macromolecules, Ch. VIII, sect. 5, *Naturwissenschaften* (in the press).

Russian Crystals

Symmetry of Crystals. By E. S. Fedorov. Translated from the Russian by David and Katherine Harker. Pp. x+315. (American Crystallographic Association: New York, 1971.) \$25.00.

ONE of the great scientific activities of the nineteenth century was classification. In many fields the systems then developed have long since fallen into disuse, but the most modern work in X-ray diffraction still makes use of the idea of the crystallographic space groups which were discovered, apparently independently, by Fedorov somewhere between 1885 and 1890, by Schoenflies in 1891, and by Barlow in 1894. Unfortunately, because Fedorov's work was published in Russian, it did not become widely recognized in the West until after the other two publications. The three authors approach the subject from quite different points of view and Fedorov's is based on a geometrical system of his own development which involves consideration of the ways in which space may be filled by polyhedra of different shapes.

In 1949 the USSR Academy of

Sciences commissioned the publication of a collection of Fedorov's contributions divided into five monographs. The first three set up the basic analytical geometry required and consider the necessary ideas of symmetry. Monograph four is Fedorov's own comparison with the results of Schoenflies, and in monograph five Fedorov develops the ideas of space-filling polyhedra.

The present work is a translation of the 1949 Russian text and is obviously a labour of love. The project was undertaken by the National Science Foundation and the American Crystallographic Association, and it goes without saying that a work of this magnitude and complexity could not possibly have been translated adequately except by someone as familiar with the scientific material as with the Russian language. Dr and Mrs Harker clearly satisfy these conditions and their magnificent version is a real contribution to the historical documentation of crystallography.

It is, however, very much more than a mere historical document. The ideas and developments followed by Fedorov are most stimulating though the somewhat ponderous prose—which undoubtedly is an accurate reflexion of the nineteenth century atmosphere—may be a little daunting to some readers.

It should certainly find a place in the libraries of all crystallographic laboratories, and all concerned in its production are to be congratulated on making such a fascinating document readily available to modern crystallographers.

C. A. TAYLOR

Narcotic Pharmacology

Narcotic Drugs: Biochemical Pharmacology. By Doris H. Clouet. Pp. xxii+506. (Plenum: New York and London, 1971.) \$31.36.

ALTHOUGH the opium alkaloids have been used for medicinal purposes in one form or other for more than two thousand years, we still do not understand how these drugs and their modern synthetic and semi-synthetic congeners exert their analgesic action and why they produce such severe physical dependence even after a relatively short period of use. In recent years, the interest in these drugs has risen steeply, chiefly because of their widespread non-medicinal use by persons who have become dependent on them. A great deal of effort has been spent by research workers in universities, research institutes and pharmaceutical firms to produce new compounds which retain their analgesic power but are not liable to be abused as drugs of addiction.

The volume edited by Dr Clouet brings together some of the work published in recent years. The subtitle of

Biochemical Pharmacology is rather a misnomer because the twenty-six chapters range over a much wider area of the pharmacology of the narcotic analgesic drugs than could be defined as biochemical. The contents cover the chemistry of narcotic analgesic drugs, their metabolic disposal, their effects on the metabolism of energy, phospholipids, proteins and nucleic acids, their effects on biogenic amines, acetylcholine, corticosteroids and other hormones. The sites and modes of action of the narcotic analgesic drugs are examined in single cells, the central and peripheral nervous system and the kidneys. There is a discussion of the possible causes of tolerance and, finally, a consideration of two important therapeutic programmes, namely the use of antagonists as a protective measure and the methadone maintenance programme.

It is unfortunate that most of the research work reported in this volume was published before naloxone, the first pure antagonist of morphine, had become available. In many of the papers quoted, the partial agonists, nalorphine and levallorphan, served as "antagonists"; because of their dual action as agonist and antagonist, the interpretation of the experiments in which they were used was often equivocal. Until the advent of naloxone, it was not easy to distinguish between specific and non-specific effects of morphine-like drugs. This dilemma was particularly difficult to overcome in experiments on certain isolated tissues in which only very high concentrations of these drugs had an effect. We know now that many of these effects are non-specific; apart from not being antagonized by naloxone they also do not show such stereospecificity as is found for their analgesic effects. It is for these reasons that some of the observations and conclusions presented in the volume cannot be accepted as valid.

The editing of books written by a number of authors is a difficult task of which Dr Clouet has absolved herself well. Nevertheless, a few unfortunate phrases have not been expunged, as for example "illicit narcotic seizures also have been analysed by microcrystal tests".

My criticisms should, however, not detract from the importance of this book which will be of great value to the active research worker who feels with L. Shuster that "theoretical castles are easy to build in the realm of narcotic addiction" and with H. L. Borison that "so long as we lack more effective means of studying the communication mechanisms of the brain, we shall have to face the dilemma as to how the neurochemical approach to addiction can yield meaningful answers if they do not rest upon sound neurophysiological footing".

H. W. KOSTERLITZ

CORRESPONDENCE

Space Research

SIR,—May I as one of the founder members of the European Space Research Institute (ESRIN) at Frascati, Rome, thank you for bringing to the attention of your readers the dangers facing that institute. A proposal to close the institute was accepted as part of the basic plan for the future programme by the council of ESRO of July 14 subject to definite adoption in November. This action has been widely considered as a setback to the cause of European scientific collaboration.

This situation is of importance at this moment when there is a probability of growing collaboration in Europe and I would like to consider it in the light of Professor Sir Brian Flowers's recent article in *Nature* on "Science and the Common Market". In this article he proposed five criteria for successful collaboration in science. For brevity I shall paraphrase these five criteria as follows: (a) the need to establish a scientifically viable institute; (b) that the institute should have a part to play in European science; (c) that it should be supported wholeheartedly by the collaborating nations.

Let me now consider to what extent ESRIN has satisfied these criteria. Those of us who worked together to build ESRIN believed that there was a need for a European institute devoted to space physics and that ESRIN could fulfil that need despite the severe restriction imposed on it that any direct participation in satellite or rocket experiments was precluded. The contributions

made to the field of space physics are exemplified by the following: theoretical studies of the magnetosphere, laboratory simulation of magnetospheric and ionospheric phenomena, collaboration in European experiments on gravitational waves and in design of a cosmological satellite experiment; studies of the solar corona with reference to heating mechanisms and spectroscopic observations; development of a high resolution laser scattering technique for atmospheric studies; design of a new high aperture, high resolution electrostatic spectrograph for particle analysis in the ionosphere and of novel multichannel recording systems (patented); and so on.

I believe that the breadth and depth of these contributions indicate that in less than three years of full operation ESRIN has achieved a high degree of viability. Perhaps this is best demonstrated by the fact that protests against the proposed closure have been made by many scientists including Professor Alfvén, Professor Biermann, Professor Lehn, Professor Parker and Professor Van Bueren.

The programme, and the budgetary means to carry it out, have also been approved by the council of ESRO each year up to and including 1971. Why then has it been considered that this viable and internationally recognized institute should be closed; that in the future ESRO cannot support its budget of \$2 million out of a scientific research budget of \$27 million and a total budget of \$70–80 million?

The new plans for ESRO indicate a

changing programme for the organization as a whole and it is reasonable to expect the programmes of each part of ESRO to reflect these changes. Not to allow this to take place at ESRIN, but to abandon the capabilities to carry out research on the European scale built up at considerable expense to the taxpayer, would appear to be an act of irresponsibility.

It seems to me therefore that the explanation for the action lies more deeply than this change in programme. I believe it arises from the problem of "in house" research which has dogged not only ESRIN, but ESRO, from the start. The policies being evolved for execution of the new programme call for further reductions of "in house" research; the closure of ESRIN would be but one of the reductions.

Surely, as stated by Sir Brian Flowers in his article, the lesson of the success of CERN is that it has satisfied his five criteria and that the success is due in part to the complete collaboration and support of a central research laboratory and research group, that is, of "in house" research.

In choosing not to follow the example of CERN, and, in doing so, to close one of its viable and internationally recognized research centres, ESRO will find it more difficult to retain its own viability as a research organization.

Yours faithfully,

T. S. GREEN

*Culham Laboratory,
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Obituary

Professor Asher Korner



ON September 22, Professor Asher Korner died after some months of illness at the age of forty-four. Since 1967 he was Professor of Biochemistry in the School of Biological Sciences at Sussex University. He started his research career as a graduate student in the Department of Biochemistry at Cambridge working with Professor F. G. Young on the influence of androgens on growth. During the course of this work he became in the early fifties one of the pioneers developing cell-free systems capable of incorporation of amino-acids into protein. By the mid-fifties he had shown that microsomes from hypophysectomized rats were deficient in their protein synthesizing capacity and that this deficiency could be rapidly reversed by an injection of growth hormone to the whole animal.

He went on to develop the first cell-free system from rat liver consisting of ribosomes freed from membranes and cell sap, which was capable of protein synthesis, and with this system he showed that the lesion in hypophysectomized animals lay in the ribosome fraction.

In the early sixties with the development of the messenger RNA concept it seemed that the effects of growth hormone on protein synthesis and growth could be explained in terms of its control of messenger RNA synthesis. Careful detailed research showed repeated inconsistencies in this model. By the mid-sixties his working hypothesis for the control by growth hormone was that this control was affected at the point of initiation of new rounds of protein synthesis on messenger RNA molecules. He thus became one of the first expo-

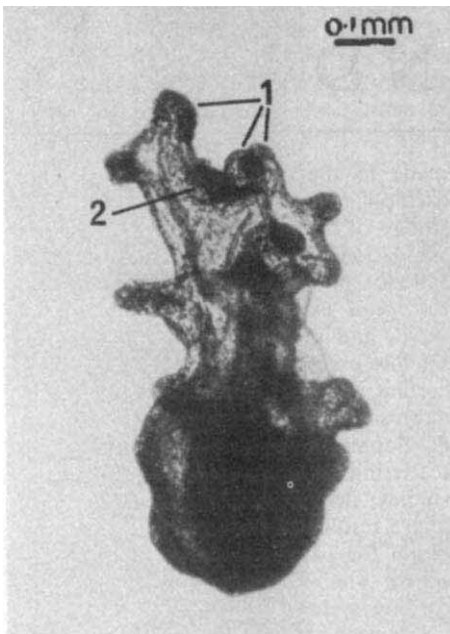
nents of the new popular concept of controls on protein synthesis at the cytoplasmic level. Further he believed that the effects of growth hormone on RNA synthesis were secondary to its effects on protein synthesis. These concepts were the basis for his most recent research on the mechanism of initiation of protein synthesis and the interrelationship between protein and RNA synthesis. In summary he has made a major contribution to the development of the ideas and concepts which are now known as molecular biology and their application to the field of hormonal control of protein and nucleic acid metabolism, particularly the control of protein synthesis brought about by growth hormone.

Apart from his personal research achievements Asher Korner was an able and inspiring teacher both of graduates and undergraduates. His style of research, knowledge and enthusiasm helped the many graduates, students and associates who worked with him. His leadership created an environment in which learning and research flourished. In 1967 he left Cambridge to become the first Professor of Biochemistry at Sussex University where he quickly established a flourishing group of young and able biochemists.

Above all Asher Korner was an unusually kind and generous person. His loss is a blow to science in general but these personal qualities make his death particularly tragic to those who knew him well.

Erratum

In the article "Larval Development and Metamorphosis of *Acanthaster planci* (Asteroidea)" by J. A. Henderson and J. S. Lucas (*Nature*, 232, 656; 1971), Fig. 2 should have been as follows:



Reports and Publications

not included in the Monthly Books Supplement

Great Britain

- Proceedings of the Royal Irish Academy. Vol. 71, Section B, No. 8: The Granite Dome of the Upper Liffey Valley District, Co. Wicklow—a Subsidiary Unit of the Leinster Batholith. By J. C. Brindley. Pp. 109–118+plate 4. (Dublin: Royal Irish Academy, 1971.) 18p. [267]
- The Leicester Polytechnic Students Oksfjord Expedition 1970. Loppa Peninsula, Finnmark, Arctic Norway. Official Report. Pp. 94. (Leicester: City of Leicester Polytechnic, 1971.) [267]
- Whatman Advanced Ion-Exchange Celluloses—Guide to Literature. Pp. ii+72. (Maidstone: W. and R. Balston (Modified Cellulose), Ltd., Springfield Mill, 1971.) 18p. [267]
- Overseas Development Institute. Annual Report 1970. Pp. 41. (London: Overseas Development Institute, Ltd., 1971.) [267]
- Medicines Commission. First Annual Report to end of 1970. Pp. iv+12. (London: HMSO, 1971.) 124p net. [277]
- Department of Education and Science. Education Survey No. 13: The Education of Immigrants. Pp. v+129+13 photographs. (London: HMSO, 1971.) 85p net. [287]
- Pulse Shape Discrimination with Organic Scintillators. By Dr. G. W. McBeth, R. A. Winyard and J. E. Lutkin. Pp. 27. (Colnbrook, Bucks: Koch-Light Laboratories, Ltd., 1971.) [287]
- Population of the United Kingdom—Report of the Select Committee on Science and Technology, Session 1970–71. Observations by the Government. (Cmd. 4748.) Pp. 3. (London: HMSO, 1971.) 5p net. [297]

- Home-Grown Cereals Authority. Progress Reports on Research and Development, 1970/71. Pp. 43. (London: Home-Grown Cereals Authority, 1971.) [307]
- Potato Marketing Board. The Production of Potatoes for Canning. By D. Gray and J. K. A. Bleasdale. Edited by Miss V. E. Ellis. Pp. 26. (London: Potato Marketing Board, 1971.) [307]
- International Journal for Parasitology, Vol. 1, No. 1, May 1971. Edited by Professor J. D. Smyth. Pp. 1–108. Annual subscriptions (including postage): For libraries, research establishments and all other multiple-reader institutes £10; \$25. Private individuals, whose departmental libraries subscribe, may obtain this journal for their personal use at a reduced rate of £6; \$15. (Oxford and New York: Pergamon Press, 1971.) [307]
- EMI and International Defence. Pp. 20. (Hayes, Middx.: EMI Electronics, Ltd., 1971.) [307]
- Building Research Station Digest, No. 132: Wilful Damage on Housing Estates. Pp. 4. (London: HMSO, 1971.) 5p. [307]

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- Transvaal Museum, Pretoria. Report for the year ending 31st March 1970. Pp. 32. (Pretoria: Transvaal Museum, 1971.) [217]
- Ontario Research Foundation. 1970 Annual Report. Pp. 44. (Sheridan Park, Ontario: Ontario Research Foundation, 1971.) [227]
- The Rockefeller Foundation. President's Review and Annual Report for 1970. Pp. xxviii+229. (New York: The Rockefeller Foundation, 1971.) [237]
- National Research Council of Canada. Report of the President 1970–71. Pp. 94. (Ottawa: National Research Council of Canada, 1971.) [237]
- Cornell International Agricultural Development Bulletin No. 21: Feasibility of Commercial Dairying with Cattle Indigenous to the Tropics. By R. E. McDowell. Pp. 22. (Ithaca, New York: New York State College of Agriculture, Cornell University, 1971.) \$0.35. [237]
- BC Research. 27th Annual Report 1970. Pp. 20. (Vancouver: British Columbia Research Council, 1971.) [237]
- Board of Grain Commissioners for Canada, Winnipeg, Manitoba. Grain Research Laboratory—1970 Report. Pp. v+87. (Ottawa: Information Canada, 1971.) [267]
- World Health Organization. Technical Report Series, No. 465: Application and Dispersal of Pesticides—Eighteenth Report of the WHO Expert Committee on Insecticides. Pp. 66. (Geneva: WHO; London: HMSO, 1971.) 4 Sw. francs; 40p; \$1.25. [267]
- Government of India: Ministry of Health. Report of the Central Drugs Laboratory, Calcutta, 1st April 1962 to 31st March 1965. Pp. ii+60. (Delhi: Manager of Publications, 1970.) 73p. [267]
- Journal of Fluorine Chemistry, Vol. 1, No. 1, July 1971. Edited by H. J. Emeleus and J. C. Tatlow. Pp. 1–128. Published quarterly. Subscription rate: Sfr. 114.75; US\$ 28.70 per year, including postage. (Lausanne: Elsevier Sequoia, SA., 1971.) [267]
- South African Journal of Antarctic Research, No. 1, 1971. Pp. 1–40. Published annually. Subscription rate: R2.00 per annum. (Pretoria: Publishing Division, South African Council for Scientific and Industrial Research, POB 395, 1971.) [267]
- Neurobiology, Vol. 1, No. 1, 1971. Pp. 1–67. Subscription price: D.kr. 148 plus postage D.kr. 12—(\$21.50) payable in advance. Price per issue D.kr. 40—(\$5.40). (Copenhagen: Munksgaard, 1971.) [287]
- Australian Journal of Botany: Supplementary Series, Supplement No. 1: Morphology and Taxonomy of the *Audouinella* Complex (Rhodophyta) in Southern Australia. By W. J. Woelkerling. Pp. 91. (East Melbourne: Editorial and Publications Section, CSIRO, 1971.) [287]

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